American Heart Journal

An international publication for the study of the circulation

GEORGE E. BURCH M D
Editor
HARRY L. COLCOLOUGH M D
NICHOLAS P DePASQUALE, M D
JOHN H PHILLIPS, M D
Assistant editors
1430 Tulane Avenue New Orleans La. 70112
The C V Mosby Company 11830 Westline Industrial Drive St Louis Mo 63141

VOLUME 81

JANUARY JUNE 1971

VOLUME 81

Printed in the United States of America

American Heart Journal

JANUARY 1971

Contents

Editorial

Clinical communications

Experimental and laboratory reports

continued on page 5

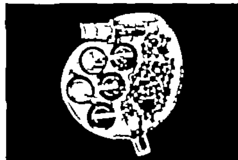
"Waiting to be of help"

Cardiac Pacemakers by Medtronic come in a variety of models When you select a pacemaker Medtronic is there to help you become familiar with pacemaker options options that enable you to match your patient s indications with a specific unit When you need a pacemaker in a matter of hours Medtronic delivers When you request assistance with technical problems that may arise during the procedure Medtronic is there to help

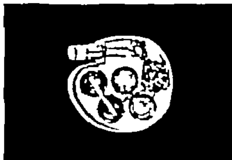
Throughout the country Medtronic s highly trained representatives are committed to give this kind of help and cooperation. In addition Medtronic s staff of medical and technical consultants is available 24 hours every day for consultatio Obtaining help is simply a matter of calling 612 781 6061 colle

But help does not end here. Medtronic will supply you with regularly updated, computerized follow up data on your pacemake patients Medtronic analyzes returned units conducts educational seminars for paramedical personnel and mails to physicians a bimonthly publication containing practical hints reliability reports and other information related to pacemaking.

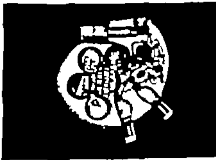
Medtronic is waiting to be of help Call on us at any time



Medtronic™ Chardack™ Model 5842 Implantable Demand Pacemaker of the ventricular inhibited type.



Medtronic™ Chardack™ Model 5862 Implantable Asynchronous Pacemaker with fixed rate and amplitude



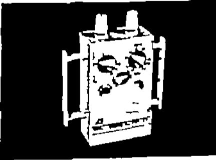
Medtronic™ Chardack™ Model 5870 Implantable Asynchronous Pacemaker with adjustable rate and amplitude



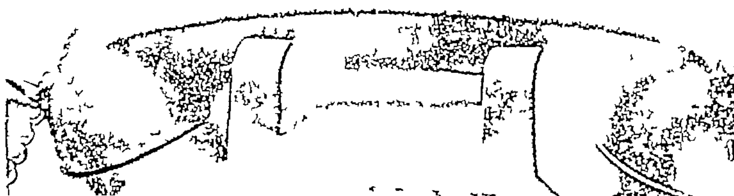
Medtronic, Inc



Medtronic™ Chardack™ Model 5858 Implantable Pediatric Pacemaker Asynchronous, nonadjustable, unipolar



Medtronic™ Model 5880 External Demand Pacemaker of the ventricular inhibited type Adjustable rate amplitude, and sensitivity



Contents *continued*

continued on page 7

Vol. 81, No. 1, January, 1971. American Heart Journal is published monthly by The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Mo. 631[illegible].
Annual subscription rates.

	U.S.	Canada, [illegible]	Other countries
Institutional*	$[illegible]	$26.00	$27.00
Personal†	$15.50	$21.00	$22.00
Students, interns, residents†	$12.95	$15.45	$16.45

Single copies are $2.50 prepaid. Remittances should be made by check, draft, post office or express money order payable to this Journal.
*Institutional (multiple reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics, city, county, state, provincial and national government bureaus and departments, and all commercial and private institutions and organizations.
†Personal subscriptions and all student-rate subscriptions must be in the name of, and billed to, individuals.

Subscriptions may begin at any time.
Second class postage paid at St. Louis, Mo.

Contents *continued*

Fundamentals of clinical cardiology

Appraisal and reappraisal of cardiac therapy

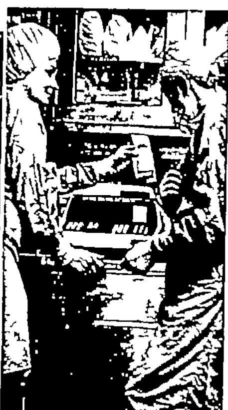
Annotations

Letters to the Editor

Book reviews

Emancipate your time





Calculate Stroke Volume, Total Peripheral Resistance, And Cardiac Output In Less Than Two Minutes With The HP Calculator System 9100

The large amount of data generated during a catheterization can be a problem. It has to be reduced quickly and accurately for evaluation by the cardiologist.

The Hewlett Packard Calculator System 9100 solves this problem. It fits into your lab, so you can compute cardio-vascular data as it becomes available. You'll no longer have to perform mechanical computations, or wait in line to get on the big computer. If computations on the 9100 indicate further testing, you can proceed immediately and avoid rescheduling the lab, personnel, and patient.

Your lab computing system begins with the HP 9100B Programmable Calculator – a machine that combines the low cost and operating ease of a calculator with the memory of a computer. All operations are straightforward – performed in standard scientific/statistical notation, with no foreign computer language to learn. You can enter data and programs via the keyboard, for instant entry, you can store often-used programs on handy magnetic cards.

System 9100 is backed by fully documented program packages. For instance, the **new HP Cardiology Program PAC** and the new Stat-PAC contain *applied* biomedical and statistical programs that will help speed your data analysis for diagnosis.

Get computer capability for your lab. You can put the System 9100 to work *immediately* for less than $1.11 per computing hour. Purchase, lease, and rental options available. For further information or to arrange a "hands on" demonstration at your desk, write: Hewlett Packard, P.O. Box 301, Loveland, Colorado 80537

HEWLETT hp PACKARD

HP CALCULATOR SYSTEM 9100

American Heart Journal

FEBRUARY 1971

Contents

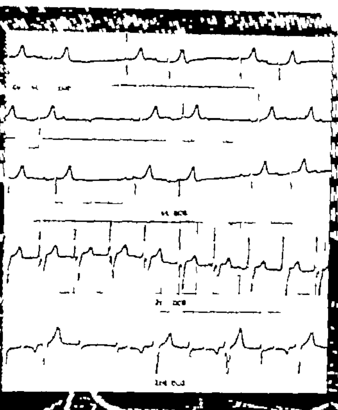
Editorial

Clinical communications

Experimental and laboratory reports

continued on page 5





HOLTER DCG MONITOR CASE HISTORY NO. 5

This 80-year-old vigorous and active male was presented with two to week history of recurrent episodes of brief darkening of vision associated with sensation of light headedness. He noted progressive decrease in previously excellent exercise tolerance at the same time. There was no history of hypertension, chest pain, palpitation or decompensation. He required no cardiac drugs in the past.

On physical examination, his blood pressure was 170/90 without orthostatic hypotension. The routine electrocardiogram disclosed Wenckebach mechanism. The initial dynamic electrocardiogram demonstrated Wenckebach periods, an average to slow ventricular rate and in addition, intermittent first degree AV block, blocked atrial premature beat, and sinus pauses. The second dynamic electrocardiogram demonstrated the presence of normally functioning transvenous demand pacemaker which had been inserted in the interim. The third dynamic electrocardiogram obtained three months later demonstrated pacemaker malfunction due to late displacement of the catheter tip with failure of both inhibition and intermittent failure to capture. As result of this study the patient was re-hospitalized, the catheter was re-positioned and normal demand pacemaker function was restored.

Now, for less than $2,000, you can have a Holter Monitoring System and make continuous, 12-Hour, DCG recordings!

Modern heart monitoring equipment is no longer an expensive luxury. Now any doctor can afford the same advanced equipment used by prominent cardiologists and teaching institutions. He can make continuous dynamic electrocardiographic recordings of his patients for periods up to 12 hours as they go about their daily out patient activities and he can use the inexpensive services of a qualified DCG screening center to scan the recordings.

Every physician knows the limitations of the typical ECG record measuring only 50 to 100 heart beats. He knows that good diagnostic procedure frequently dictates the need for larger samples taken during normal activities. Now for less than $2000 he can obtain a basic Dynamic Electrocardiographic System from Avionics. It includes the Electrocardiocorder — a small unique portable tape recorder — and the associated instrumentation. It includes everything that the physician needs to provide his patients with the safeguards of Holter DCG monitoring immediately.

And for those who purchase the basic system but do not wish to invest in the more-expensive high-speed scanning and printout equipment — Avionics will provide referral to a specialized quality-controlled, DCG screening center where reliable scanning services are available for modest fees.

If you would like to know more about the Avionics equipment or the screening services — simply send in the coupon and you will receive a fully illustrated color brochure.



AVIONICS RESEARCH PRODUCTS
division of Del Mar Engineering Laboratories
6901 West Imperial Highway
Los Angeles, California 90045
Phone (213) 641-6334

AVIONICS RESEARCH PRODUCTS
6901 W. IMPERIAL HIGHWAY
LOS ANGELES, CALIF. 90045

☐ Please send me the literature. I would like to know more about Holter monitoring and the Avionics Dynamic Electrocardiographic Systems presently being employed by cardiologists and general practitioners.

☐ Send the literature and schedule me for a visiting demonstration. I am definitely interested in acquiring this kind of equipment.

☐ Please refer me to a specialized quality-controlled screening center.

Name

Title & Specialization

Address

City

State

Contents *continued*

continued on page 7

Vol. 81, No. 2, February 1971. American Heart Journal is published monthly by The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Mo. 63141.

Annual subscription rates

	U.S.	Canada, Mexico	Other countries
Institutional*	$[illegible]	$36.00	$37.00
Personal†	$[illegible]	$21.00	$22.00
Student, intern, resident†	$12.95	$13.45	$1[illegible].45

Single copies are $1.50 postpaid. Remittances should be made by check, draft, post office or express money order payable to this Journal.

*Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics, city, county, state, provincial and national government bureaus and departments, and all commercial and private institutions and organizations.

†Personal subscriptions and all student-rate subscriptions must be in the names of, and billed to, individuals.

Subscriptions may begin at any time.
Second class postage paid at St. Louis, Mo.

potassium cannot be com letely repaired unless chloride is made vailable * KAY CIEL ELIXIR (potassium hloride) restores and maintains the elec olyte balance

ay Ciel Elixir is potassium chloride the pre- rred salt—chloride ion is necessary for op- mum retention and utilization of potassium the cellular level

ay Ciel Elixir is a liquid the preferred form -provides usable potassium and chloride for ster more dependable absorption with min nal risk of gastrointestinal irritation

ay Ciel Elixir is sugar free and cherry avored the preferred taste—so pal able it can be diluted with water one

ay Ciel Elixir provides uniform qual y to aid in insuring continued patient cceptance

KAY CIEL ELIXIR
POTASSIUM CHLORIDE 10%)



And it tastes good too!

Side Effects Vomiting, nausea abdominal d scomfort and diarrhea may occur Symptoms and igns of potassium intoxication include listlessness mental confusion par esthesia of the extremities, weakness of the legs flaccid paralysis fall in blood pressure cardiac arrhythmias, and heart block. *When hyperkalemia exists it should be* promptly treated with the discontinuance of potassium adm nistration or other st ps to lower serum levels if ind cated since sudden shift in plasma levels may induce potentially dangerous card ac arrhythmias. **Dosage and Administration:** Adults one tablespoonful (15 cc.) d luted in one glass of water twice daily after the morning and evening meal *Patients should be cautioned to follow directions expl itly in regard to d lution of Kay Ciel Elixir to prevent ga trointestinal injury* **How Supplied:** Bottles of one pint and one gallon. **Composition.** Each 15 cc. (one tablespoonful) contains potassium chloride 1 5 Gm. supplying 20 mEq of elemental potassium. **Contraindications.** Impaired renal funtion untreated *Addison s Disease dehydration heat cramp and hyperkalemia.* **Precautions.** Should be administ red with caution and adjusted to the requirements of the individual pat ent since the amount of deficiency and corresponding daily dose is often not known E cessive or even therapeutic dosages may result in potassium intoxication *Patients should be frequently checked and* period c ECG and/or plasma potassium levels made High plasma concent ations of potas sium ion may cause card ac depression, arrhythmias or arrest Use w th caut on in patients with cardiac d sease In hypokalemic states attention should be directed toward the *correction of the frequently associated hypochloremic alkalosis*

Welt L. G In Goodman L A and Gilman A. eds., The Pharmacological Basis of Therapeutics ed 3 New York The MacMillan Co 1965, p. 790.

POTASSIUM...
IN BALANCE OR IMBALANCE?

When optimum retention and utilization
of potassium are essential
Kay Ciel (potassium chloride)

Contents *continued*

cannot be completely repaired unless chloride is made available. * KAY CIEL ELIXIR (potassium chloride) restores and maintains the electrolyte balance.

Kay Ciel Elixir is potassium chloride the preferred salt—chloride ion is necessary for optimum retention and utilization of potassium the cellular level

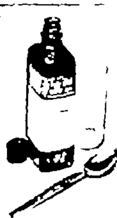
Kay Ciel Elixir is a liquid the preferred form provides usable potassium and chloride for faster more dependable absorption with minimal risk of gastrointestinal irritation

Kay Ciel Elixir is sugar free and cherry flavored the preferred taste—so palatable it can be diluted with water alone

Kay Ciel Elixir provides uniform quality to aid in insuring continued patient acceptance

KAY CIEL ELIXIR

(POTASSIUM CHLORIDE 10%)



And it tastes good too!

Side Effects. Vomiting, nausea abdominal discomfort and diarrhea may occur Symptoms and signs of potassium intoxication include listlessness mental confusion, paresthesia of the extremities, weakness of the legs flaccid paralysis, fall in blood pressure cardiac arrhythmias, and heart block When hyperkalemia exists, it should be promptly treated with the discontinuance of potassium administration or other steps to lower serum levels if indicated since sudden shift in plasma levels may induce potentially dangerous cardiac arrhythmias **Dosage and Administration** Adults one tablespoonful (15 cc.) diluted in one glass of water twice daily after the morning and evening meal. Patients should be cautioned to follow directions explicitly in regard to dilution of Kay Ciel Elixir to prevent gastrointestinal injury **How Supplied.** Bottles of one pint and one gallon **Composition** Each 15 cc (one tablespoonful) contains potassium chloride 1 5 Gm supplying 20 mEq of elemental potassium. **Contraindications.** Impaired renal funtion untreated Addison's Disease dehydration, heat cramps, and hyperkalemia. **Precautions** Should be administered with caution and adjusted to the requirements of the individual patient since the amount of deficiency and corresponding daily dose is often not known Excessive or even therapeutic dosages may result in potassium intoxication. Patients should be frequently checked and periodic ECG and/or plasma potassium levels made High plasma concentrations of potassium ion may cause cardiac depression arrhythmias or arrest Use with caution in patients with cardiac disease In hypokalemic states attention should be directed toward the correction of the frequently associated hypochloremic alkalosis

*Welt, L G In Goodman L A and Gilman, A., eds., The Pharmacological Basis of Therapeutics ed 3 New York The MacMillan Co 1965, p. 790.

POTASSIUM... IN BALANCE OR IMBALANCE?

When optimum retention and utilization of potassium are essential Kay Ciel (potassium chloride) restores and maintains the electrolyte balance



Cooper Laboratories, Inc. Mystic Conn 0635

American Heart Journal

MARCH 1971

Contents

continued on page 6

Mode of Action: Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

Indications: *Sublingual and Chewable:* For the prevention and treatment of angina pectoris.

Oral: For the relief of angina pectoris. It is not intended to abort the acute anginal episode. SORBITRATE WITH PHENOBARBITAL is indicated for patients in whom the angina pectoris is accompanied by anxiety or its related symptoms.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety Phenobarbital may be habit forming.

Precautions. Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the head aches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension, individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect) drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration. *Route:* Sublingual oral nd chewable tablets.

Individual Dose. To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 10 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg Sublingually or orally 5 to 10 mg. is the range commonly used although doses of up to 30 mg have frequently been employed.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals, Oral SORBITRATE may be taken 3 to 4 times daily Chewable SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily Although the onset and duration of effect of coronary nitrates may vary following are the generally reported ranges of these values for SORBITRATE:

Onset of Effect Sublingual and Chewable: 2 to 5 minutes. Oral. 15 to 30 minutes.

Duration of Effect: Sublingual and Chewable 1 to 2 hours. Oral Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.



STUART PHARMACEUTICALS | Pasadena, Calif 91109
Division of ATLAS CHEMICAL INDUSTRIES, INC.

Review

Fundamentals of clinical cardiology

Appraisal and reappraisal of cardiac therapy

Annotations

Letters to the Editor

Book reviews



Eat to your heart's content.

at we eat depends on
y we eat. Whether it be
pleasure, for nourishment,
ust to keep trim. But how
ny of us eat for our heart's
efit?
According to latest medical opin-
a low-saturated-fat, low-cholesterol
is still one of the best ways to a man's
rt.
uch diets invariably include a vegetable oil margarine—
Fleischmann's. Why? Because Fleischmann's is made
n 100% corn oil, and no vegetable oil lowers serum
esterol better than corn oil. No margarine tastes better
r. Fleischmann's has that light, distinctive flavor that has
ed make it America's favorite premium margarine.
rike a blow for better diets. Invite Fleischmann's to din-
ner. And breakfast. And lunch.
It might do your heart good.

P.S. If you're interested in the variety of service material Fleischmann's offers doctors and their patients, write Fleischmann's Margarines, Box 46F, Mount Vernon, N.Y. 10559. No other margarine manufacturer is better equipped to serve you in this field.

Fleischmann's Margarines

made from 100% corn oil. Fleischmann's comes Lightly Salted, Unsalted, and Soft. And for half the calories, all the fat of regular margarines, try delicious Diet Fl

American Heart Journal

APRIL 1971

Contents

continued on page 5

Treat failing hearts gently.

DIAMOX furnishes the mild diuretic action needed in many cases of congestive heart failure Its gentle action in maintaining fluid loss is ideal in long term therapy A single 250 mg tablet in the morning provides peak action during the daytime hours And affords your patient an uninterrupted night s sleep Best results are often obtained with therapy of 2 days interrupted by a day s rest and repeating—or merely by giving DIAMOX Tablets every other day

Prescribe DIAMOX for gentle dependable diuresis



Contraindications — Situations in which sodium and/or potassium serum levels are depressed In kidney and liver disease or dysfunction suprarenal gland failure and hyperchloremic acidosis Long-term administration is contraindicated in chronic noncongestive angle closure glaucoma

Warning—Although teratogenic and embryocidal effects demonstrated in mice at more than ten times the equivalent therapeutic doses have not been evidenced in humans, DIAMOX Acetazolamide should not be used in pregnancy especially during the first trimester unless the expected benefits outweigh these potential adverse effects.

Precautions—Increasing the dose may increase drowsiness and paresthesia and decrease diuresis. Reactions common to sulfonamides may occur fever rash crystalluria, renal calculus, bone marrow depression, thrombocytopenic purpura hemolytic anemia, leukopenia, pancytopenia agranulocytosis If such occur discontinue drug and institute appropriate therapy

Side Effects—During short term therapy: paresthesias loss of appetite polydrowsiness, confusion In long-term therapy an acidotic state may supervene Transient myopia has been reported Other occasional reactions urticaria melena, hematuria, glycosuria hepatic insufficiency flaccid paralysis, convulsions.

DIAMOX® 250 mg
Acetazolamide Tablets

LEDERLE LABORA... of
American Cyanamid Co

Contents *continued*

continued on page 7

Vol. 81 No. 4, April, 1971 The American Heart Journal is published monthly by The C. V Mosby Company 11830 Westline Industrial Drive, St. Louis, Mo. 63141.

Annual subscription rates.

	U.S.	*Canada, Mexico*	*Other countries*
Institutional*	$21.00	$24.00	$27.00
Personal†	$ [illegible]	$21.00	$22.00
Student, intern, resident†	$12.95	$15.45	$16.45

Single copies are $1.50 postpaid. Remittances should be made by check, draft, post office or express money order payable to this Journal.

*Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics, city, county, state, provincial and national government bureaus and departments, and all commercial and private institutions and organizations.

†Personal subscriptions and all student rate subscriptions must be in the names of, and billed to, individuals.

Subscriptions may begin at any time.

Second class postage paid at St. Louis, Mo.

Dyrenium®

brand of triamterene

potassium-conserving diuretic

for edema due to certain causes*

Action Is Independent of Aldosterone Levels

Dyrenium is not an aldosterone antagonist and its actions are not affected by the level of aldosterone The dosage need not be increased as the aldosterone level rises

Each capsule contains 100 mg of triamterene.

Before prescribing see complete prescribing information in *SK&F literature or PDR*

***Indications** Edema associated with congestive heart failure, cirrhosis, nephrotic syndrome and in pregnancy; steroid-induced edema, idiopathic edema and edema due to secondary hyperaldosteronism.

Contraindications Severe or progressive kidney disease or dysfunction (possible exception nephrosis). Severe hepatic disease *Pre-existing elevated serum potassium Hypersensitivity* to the drug Continued use in developing hyperkalemia Do not give potassium supplements, either by drug or by diet

Warnings Observe regularly for possible blood dyscrasias liver damage or other idiosyncratic reactions Blood dyscrasias have been reported Check BUN and serum potassium periodically especially in the elderly and those with suspected or confirmed renal insufficiency Use [illegible] pregnancy only when essential to patient welfare

Precautions If hyperkalemia develops, withdraw the drug The following may also occur electrolyte imbalance low-salt syndrome (with low salt intake), reversible mild nitrogen retention Do periodic hematologic studies in cirrhotics with splenomegaly Concomitant use with antihypertensive drugs may result in additive potentiating effect When Dyrenium (triamterene, SK&F) is to be discontinued after intensive or prolonged therapy withdraw gradually because of possible rebound kaliuresis

Adverse Reactions Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache dry mouth, anaphylaxis, photosensitivity [illegible] elevated uric acid, rash Note Dyrenium and spironolactone are not usually used concurrently if they are, however frequent serum potassium determinations are required.

Supplied 100 mg capsules in bottles of 100

SK&F Co. Carolina, P R 00630
A subsidiary of Smith Kline & French Laboratories

('Dyrenium' is economical, too)

Contents *continued*

American Heart Journal

MAY 1971

Contents

continued on page 8

of
angina









Contents continued

Case reports

Review

Fundamentals of clinical cardiology

Appraisal and reappraisal of cardiac therapy

Annotations

continued on page 7

Vol. 81 No. 5, May 1971. The American Heart Journal is published monthly by The C. V Mosby Company 11830 Westline Industrial Drive St. Louis, Mo. 63141.
Annual subscription rates.

	U.S.	Canada, Mexico	Other countries
Institutional*	$21.50	$26.00	$27.00
Personal†	$18.50	$21.00	$22.00
Students, interns, residents†	$12.95	$15.45	$14.45

Single copies are $1.50 postpaid. Remittances should be made by check, draft post office or express money order payable to this Journal

*Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics, city county state, provincial and national government bureaus and departments and all commercial and private institutions and organizations.

†Personal subscriptions and all student-rate subscriptions must be in the names of, and billed to, individuals.

Subscriptions may begin at any time.
Second class postage paid at St. Louis Mo.

predict pacemaker failure...

by telephone

- The new Pacemaker Evaluation System by Cardiac Datacorp Inc makes it possible
- You get more accurate diagnostic data to aid you in predicting battery failure as well as determining loss of capture
- You can avoid unexpected Pacer failure and its resultant emergency complications.
- You can reduce the frequency of surgery and safely allow maximum Pacer usage
- Your patient will find it easy to use and enjoy a greater sense of security

We would be delighted to send you full information on this new trans telephonic diagnostic method. Just send us the coupon



CARDIAC DATACORP INC
DEPT CD-1C
1705 WALNUT STREET
PHILADELPHIA, PA. 19103

☐ Please have your representative call
☐ Please send me further information on Pacemaker Evaluation Systems Or call collect (215) 665-0700

NAME (Please Print)

ADDRESS

CITY

STATE ZIP

Contents continued



Lectro-pads
Lectro-pads
Lectro-pads
Lectro-pads
Lectro-pads
They work best together!

American Heart Journal

JUNE 1971

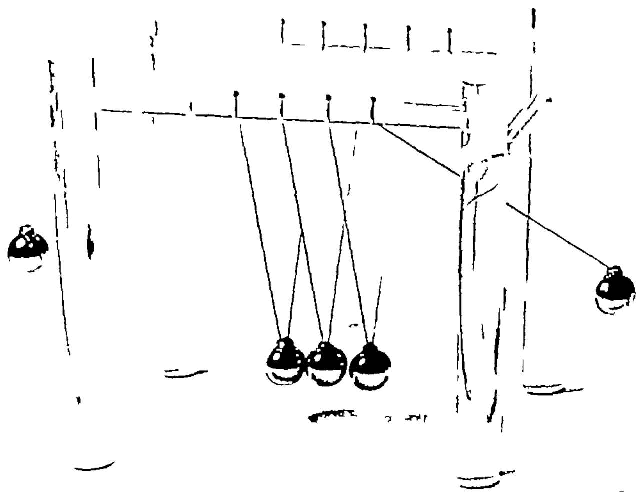
Contents

continued on page ...

Alone among antiarrhythmics...

CARDIOQUIN tablets

quinidine polygalacturonate



American Heart Journal

JUNE 1971

Contents

Editorial

Clinical communications

Experimental and laboratory reports

continued on page 5

Contents *continued*

Case reports

Clinical pathologic conference

Fundamentals of clinical cardiology

Appraisal and reappraisal of cardiac therapy

continued on page 7

Vol. 81, No. 6, June, 1971. The American Heart Journal is published monthly by The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Mo. 63141.
Annual subscription rates.

	U.S.	Canada, Mexico	Other countries
Institutional*	[illegible]	[illegible]	[illegible]
Personal†	[illegible]	$21.00	$22.00
Students, interns, residents†	$12.95	[illegible]	$14.45

Single copies are $1.50 postpaid. Remittances should be made by check, draft, post office or express money order payable to this Journal.
*Institutional (multiple reader) subscriptions are available to public and private libraries, schools, hospitals, and city, county, state, provincial and national government bureaus and departments, and all commercial and private institutions and organizations.
†Personal subscriptions and all student rate subscriptions must be in the names of, and billed to, individuals.

Subscriptions may begin at any time.
Second class postage paid at St. Louis, Mo.

—potassium depletion cannot be com
ptely repaired unless chloride is made
ailable '[a] KAY CIEL ELIXIR (potassium
loride) restores and maintains the elec
olyte balance.

y Ciel Elixir is potassium chloride the pre-
red salt—chloride ion is necessary for op-
num retention and utilization of potassium
the cellular level

y Ciel Elixir is a liquid the preferred form
provides usable potassium and chloride for
ter more dependable absorption with min
al risk of gastrointestinal irritation

y Ciel Elixir is sugar free and cherry
vored the preferred taste—so pal
ible it can be diluted with water
ne

y Ciel Elixir provides uniform qual
to aid in insuring continued patient
ceptance



AY CIEL® ELIXIR
OTASSIUM CHLORIDE 10%)

And it tastes good too!

Side Effects vom i g nausea abdominal d scomfort and d arrhea may occur Symptoms and igns of potassium into cat on include l stlessness mental confusion pa esthesia of the extrem ties weakness of the legs flaccid paralysis fall in blood pressure card a arrhythm as and heart block. When hyperkalemia e ists it should be promptly treated v th the discontinuance of potassium admin stration or other steps to lower serum levels if indicated since sudden shift in plasma levels may induce pote t ally dangerous card ac a rhythm as **Dosage and Administration** Adults one tablespoonful (15 cc) d luted in one glass of v ater tv i e daily after the morn ng and evening meal Patients should be caut oned to follow d rections expl c tly in regard to d lut on of Kay Ciel El xir to prevent gastrointest nal injury **How Supplied** Bottles of one pint and one gallon **Composition:** Each 15 cc. (one tablespoonful) contains potassi m chloride 1 5 Gm supplying 20 mEq of elemental potassium **Contraindications.** Impaired renal funt on untreated Add son s Disease dehydration heat cramps, and hyperkalem a. **Precautions.** Should be admin stered with caution and adjusted to the requirements of the individual pat ent nce the amount of deficiency and correspond ng da ly dose is often not known Exce si e or even therapeutic dosages may result in potassium intoxication. Pat ents should be frequently checked and periodic ECG and/or plasma potassium levels made H gh plasma concentrations of potassium ion may cause cardiac depression ar rhythmias or a rest Use with caution in pat ents with cardiac d sease In hypokalemic states attention should be d rected toward the correction of the frequently associated hypochlorem c alkalosis

Welt, L G In Goodman L A and Gilman A eds The Pharmacological Basis of Therapeutics, ed. 3 New York The MacM llan Co 1965, p 790

POTASSIUM... IN BALANCE OR IMBALANCE?

When optimum retention and utilization
of potassium are essential
Kay Ciel (potassium chloride)
restores and maintains the electrolyte balance

Contents *continued*

Annotations

Announcements

Index

potassium depletion cannot be completely repaired unless chloride is made available. • KAY CIEL ELIXIR (potassium chloride) restores and maintains the electrolyte balance

y Ciel Elixir is potassium chloride the preferred salt—chloride ion is necessary for optimum retention and utilization of potassium the cellular level

y Ciel Elixir is a liquid the preferred form provides usable potassium and chloride for ater more dependable absorption with minimal risk of gastrointestinal irritation

y Ciel Elixir is sugar free and cherry vored the preferred taste—so palatable it can be diluted with water ne

y Ciel Elixir provides uniform quality to aid in insuring continued patient acceptance

KAY CIEL® ELIXIR
POTASSIUM CHLORIDE 10%)



And it tastes good too!

Side Effects Von t ng nausea abdominal d scomfort and diarrhea may occur Symptoms and signs of potassium intoxicat on nclud l stlessness mental confusion, par esthesia of the e trem ties weaknes of the legs, flaccid paralys s fall in blood p es ure card ac arrhythmias, and heart block When hyperkalemia e sts it should be promptly treated with the d scontinuance of potassium admini tration or other steps to lo er erum levels if ndicated since sudden shift in plasma levels may induce pote tially da gerous ca d a arrhythm as **Dosage and Administration** Adult one t blespoonf l (15 cc) d luted in one glass of water twic daily after the morn ng and evening meal Patients should be caut oned to follow d rections e plicitly in regard to d lution of Kay C l El xir to prevent gastro ntestinal injury **How Supplied** Bottles of one pint and one gallon **Composition:** Each 15 cc (one tablespoonful) contains potassium chlo de 1 5 Gm. supplying 20 mEq of elemental potassium. **Contraindications** Impaired renal funt on untreated Add son s Disease dehydration heat cramps and hyperkalem a **Precautions.** Should be administered w th caution and adjusted to the requirements of the individual patient since the amount of def ciency and correspond ng daily dose is often not known Excess ve or even therapeut c dosages may result in potassium intoxication Pat ents should be frequently checked and periodic ECG and/or plasma potassium levels made High plasma concentrations of potassium ion may cause card ac depression, arrhythmias or arrest Use with caution in pat ents with cardiac d sease In hypokalemic states attent on should be d rected toward the correction of the frequently assoc ated hypochlo em c alkalosis

Welt L G In Goodman L A., and Gilman, A eds The Pharmacological Basis of Therapeutics ed 3 New York The MacMillan Co., 1965, p 790.

POTASSIUM...
IN BALANCE OR IMBALANCE?

When optimum retention and utilization of potassium are essential Kay Ciel (potassium chloride) restores and maintains the electrolyte balance

Contents *continued*

Annotations

Announcements

Index

potassium depletion cannot be com-
·tely repaired unless chloride is made
ailable * KAY CIEL ELIXIR (potassium
loride) restores and maintains the elec-
lyte balance.

y Ciel Elixir is potassium chloride the pre-
red salt—chloride ion is necessary for op-
ıum retention and utilization of potassium
the cellular level

y Ciel Elixir is a liquid the preferred form
provides usable potassium and chloride for
ter more dependable absorption with min
al risk of gastrointestinal irritation

y Ciel Elixir is sugar free and cherry
vored the preferred taste—so pal
ible It can be diluted with water
ne

y Ciel Elixir provides uniform qual
to aid in insuring continued patient
eptance

'AY CIEL® ELIXIR
OTASSIUM CHLORIDE 10%)



And it tastes good too!

Side Effects Vom t ng, nau ea abdominal d scomfort and d arrhea may occur Symptoms and signs of potass um intoxication include l tles ness m ntal confu ion par esthe ia of the extrem t e weakness of the legs flaccid pa alysis fall in blood pressure ca diac arrhythmia and heart block When hyperkalemia exists it should be promptly treated with the discontinuance of potassium admini tration or other steps to lower serum levels if nd cated nce sudden sh ft in plasma levels may in-duce potent ally dangerous ca d ac arrhythm as **Dosage and Administration** Adults on tablespoonful (15 cc.) d luted in one glass of water twic daily after the morn-ing and evening meal Patients should be cautioned to follow d rect ons expl c tly in regard to dil t on of Kay Ciel El x r to prevent ga trointest nal injury **How Sup-plied** Bottles of one pint and one gallon **Composition:** Each 15 cc. (one tablespoonful) contains potassium chlo-ride 1 5 Gm supplying 0 mEq of el mental potassium **Contraindications** Impa red renal f nction untreated Add on s D sease dehydrat on heat cramps and hy-perkalem a **Precautions.** Should be administered w th caution and adjusted to the requirements of the ind vidual patient since the amount of def clency and correspond ng daily dose is often not known. Excess ve or even therapeut c dos ges may result in potass um into i ation. Patients should be frequently checked and per od c ECG and/or plasma potassium levels made High plasma concentrations of potas-s um ion may cause card ac depression ar rhythmias or ar est Use with caution in pat ents with cardiac disease In hypokalemic state attention sho ld be d rected toward the correction of the frequently assoc ated hypo-chlorem c alkalos s

Welt, L. G In Goodman L A. and Gilman A eds The Pharmacological Basis of Therapeu-t cs ed 3 New York, The MacMillan Co 1965, p 790

POTASSIUM...
IN BALANCE OR IMBALANCE?

When optimum retention and utilization
of potassium are essential
Kay Ciel (potassium chloride)
restores and maintains the electrolyte balance



Contents continued

Annotations

Announcements

Index

American Heart Journal

January 1971 Volume 81 Number 1

Editorial

Assessment of cardiac pacemakers: Pacemaker frontal plane vectors

G. D. Green, B.Sc., A.Inst.P., C.Eng., F.I.E.E.
Glasgow, Scotland

The first report of the successful resuscitation of a human heart in ventricular standstill by an external electrical source was published by Zoll in 1952. By 1960[2] cardiac pacemakers were being implanted, and since that time tremendous advances have been made in this field. In fact, the implantation of a pacemaker has now become widely accepted as a method of treatment of heart block. Even patients not suffering from the extreme symptoms of syncopal attacks or Stokes-Adams attacks, who have a low rate and therefore smaller cardiac output, have been known to benefit from having a cardiac pacemaker implanted. The general feeling at the International Conference on Cardiac Pacemakers[3] in New York in November, 1968, was that whenever complete heart block with symptoms is diagnosed, a pacemaker should be implanted. Each case must evidently be judged in its own light, but the proved effectiveness of implanted cardiac pacemakers in the treatment of this disease is bound to influence future decisions in favor of implanting cardiac pacemakers.

Recent experience[4] indicates that a patient who has a pacemaker implanted can now expect two to three years of satisfactory pacing before reoperation becomes necessary. This is very different from earlier experiences of most workers in this field when pacemakers were having to be replaced after only a few months. The first internal pacemakers were of the epicardial or myocardial types in which electrodes were attached to or embedded in the left ventricle. Difficulties were experienced not only at the electrodes themselves but also with the conducting leads and their associated insulation, as well as at the junction of the leads to the generator. In 1963 the endocardial method of pacing, in which a catheter electrode is placed in the right ventricle, became the method of choice, but again earlier results were disappointing in that breaks occurred in the conducting leads, the insulation, or both within a short time of being implanted. Generator failures were common to both types of pacemaking systems and were caused by failures of electronic components or batteries. Few batteries performed satisfactorily for their predicted theoretical lifetime of three to five years.

Clinical difficulties also have occurred. Infection and extrusion of generators have been experienced as well as exit block in

From the Department of Clinical Physics and Bio-Engineering, Western Regional Hospital Board, Glasgow, Scotland.
Reprint requests to G. D. Green, Assistant Regional Physicist, Department of Clinical Physics and Bio-Engineering, Western Regional Hospital Board, West Graham St., Glasgow C. 4, Scotland.

which the pacing threshold rises above the output of the generator penetrations of the myocardium by catheter electrodes have been reported from time to time and a number of other miscellaneous difficulties have also arisen The most common difficulty with endocardial pacemakers has been displacement of the catheter electrode from its initial satisfactory position to a less satisfactory one with a consequent complete loss or an intermittent loss of pacing This has occurred at various times during the first few months after catheter insertion Remanipulation of the catheter has usually proved to be possible although in the worst circumstances a new catheter electrode has had to be used There is however some evidence (Fig 1) that after a period of time which cannot yet be specifically defined the distal end of the catheter becomes enveloped with fibrous tissue so that it becomes fixed within the ventricle

Technical faults are now rare Electrode systems will fail occasionally and there will be electronic failures from time to time though these are likely to become even rarer as more sophisticated electronics are used Battery failures in the sense of premature failure of one or more cells in a battery is however still quite common Although it is believed that great efforts are being made to overcome existing problems so that batteries will become more reliable it is also evident that other sources of power will soon be available for implantable cardiac pacemakers Isotope-powered pacemakers[6,7] and pacemakers with recharge-



Fig 1 Distal end of bipolar catheter electrode: la t 4 cm completely enveloped with fibrous tissue Catheter had been impl ted for 18 months.

able batteries have already been made and if laboratory tests and animal trials prove to be successful, there is l ttle doubt that such pacemakers with these new power sources will be used clinically in the not too distant future. However both these new types are likely to be used only in carefully selected patients in the first instance.

Some faults in pacemakers do not produce immediately obvious clinical symptoms and it is for this reason that Siddons and Sowton[18] suggested that pacemaker patients should attend pacemaker clinics at regular intervals so that both clinical and electronic checks can be made. The early detection of pacing difficulties or technical faults, including the premature failure of a cell is not only in the best interest of the patient, but it is in the long-term interest of the hospital in that it enables future action to be planned instead of emergency procedures having to be carried out, perhaps at most inconvenient times.

Many workers in this field have reported on their methods of detecting technical faults in implanted pacemakers.[17-24] The simplest technique merely relies on the minimal information provided by examination of the pacemaker pulses as seen on a standard electrocardiogram or ECG oscilloscope. X-ray examination of the patient may reveal a broken electrode or a broken conducting lead but cannot detect insulation failures. Radiographic screening may reveal a loose electrode in the myocardium which is not obvious from an x-ray. Electromagnetic radiations from a pulse generator can also be used to give ticks on a transistor radio which is placed immediately over the implanted generator. In other tests, the pulse width pulse height, pulse repetition frequency (rate) and pulse shape are all carefully observed and measured using an oscilloscope and standard electrocardiograph leads. Normal battery depletion and premature cell failures can also be detected if a suitable x-ray can be obtained of the generator while it is still implanted. Unfortunately this is somewhat difficult to achieve, and the design of some generators is such that it is impossible to x-ray all cells end on simultaneously so that an assessment of the state of individual cells may be extremely difficult.

Various methods have been used for detecting pacemaker clinical difficulties.[25-26] For instance penetration of the myocardium can be deduced from changes in the ECG while vectorcardiographic techniques have enabled changes in the direction of the catheter to be detected.

An additional technique has been used successfully in Glasgow[21,22] both for detecting technical faults and resolving clinical pacing problems. This is based on the concept of a pacemaker frontal plane vector following the concept first introduced by Einthoven and associates[27] that the electrical activity of the heart at any instant may be represented by a resultant electric dipole.

The technique is simple in principle in that the pacemaker pulses are observed and measured using a differential input oscilloscope (preferably a storage oscilloscope) and standard ECG electrodes which are placed on the patient's limbs. Consecutive measurements are made on Leads I II and III. If the "sign" of the pacemaker pulse is different from that shown on the corresponding lead of the conventional electrocardiogram the input leads to the oscilloscope should be reversed. The pulses observed on the oscilloscope will have a width according to the pulse width of the implanted pacemaker and this can be between 0.8 to 2 msec. depending on the make of pacemaker which has been implanted. The maximum pulse height, however will differ significantly from that at the pacemaker electrodes. For instance experience has shown that bipolar endocardial pacemakers produce pulses with magnitudes in the order of millivolts or tens of millivolts. On the other hand pulses obtained when bipolar myocardial electrodes are used tend to be smaller and are not greater than a few millivolts. Unipolar pacemakers, whether of the endocardial or epicardial/myocardial type give much bigger pulses, usually tens of millivolts and often over 100 millivolts in height, presumably because the electric dipole for such units is much greater than when bipolar electrodes are used. The actual

pulse shape will depend on the electronic design of the pacemaker[34] but in this technique it is not relevant unless an unusual shape quite different from previously observed shapes is suddenly observed

Whatever the type or make of pacemaker—endocardial epicardial fixed rate demand (QRS-blocking or synchronous) atrial triggered—it is possible to synthesize a pacemaker frontal plane vector from any two of a set of three pulse heights as measured on Leads I II and III respectively by using an Einthoven equilateral triangle Pure convention decrees that the QRS should be positive on Leads I and II but it may be positive or negative on Lead III This means that the resultant heart vector in the average patient when plotted on the hexaxial system points in the general direction of Lead II (about 5 o clock) Using the same sign convention and the same hexaxial system the pacemaker frontal plane vector for a bipolar endocardial pacemaker will usually point in the general direction of Lead aV_R and lies between 8 30 and 11 o clock depending on the actual position of the catheter electrode in the ventricle It has to be remembered that the electron current flow is from the negative distal electrode at the end of the catheter to the more proximal positive electrode located a centimeter or so from the tip of the catheter If the electrical connections to the catheter are reversed the pacemaker frontal plane vector will be reversed (i e rotated through 180 degrees) If the distal end of the catheter electrode is not pointing toward the apex of the heart, but instead is for instance pointing upwards the pacemaker frontal plane vector will point in a correspondingly different direction

If epicardial or myocardial electrodes have been used the direction of the pacemaker frontal plane vector will depend on the relative locations and polarities of the electrodes on the heart. With unipolar pacemakers either of the endocardial or epicardial/myocardial type the general direction of the pacemaker frontal plane vector will be given by a line joining the active electrode to the indifferent electrode sited at or near the generator

Should the insulation on either of the conducting leads of a bipolar catheter electrode break there is an alternative path for current to flow and in effect an additional electric dipole is created The resultant dipole is therefore changed in direction and this is apparent from the new direction and magnitude of the pacemaker frontal plane vector A break in the insulation on the negative conducting lead of a bipolar catheter usually results in an anticlockwise swing of the frontal plane vector while a clockwise swing is more likely when a break occurs in the positive insulation The amount of rotation in both cases will depend on where the break occurs relative to the bipolar electrodes. A break in the positive insulation will cause only a small rotation of the vector if the generator is implanted in the patient s right pectoral area It is for this reason that it has become common practice in Glasgow to implant generators in the patient s left pectoral area when any breaks in the positive insulation cause bigger clockwise rotations of the vector These arguments are understood more clearly by considering a specific chest x ray of a patient who has had an endocardial pacemaker implanted and imagining these faults and the consequences on the resultant pacemaker frontal plane vector

These theoretical arguments have been confirmed in practice in which breaks have occurred in the insulation on the negative and positive conducting leads[31,32] It is now appreciated that in certain circumstances, for instance if a generator is implanted low down in the axillary area and an insulation fault develops near the generator or if there is an S bend in the catheter within the right ventricle and a break in the insulation occurs in this part of the catheter then the vector rotations will be opposite to those given above

The same method has also been used successfully to detect a break in the conducting lead of a catheter electrode the insulation remaining intact.[33] The high impedance introduced into the pacemaker circuit by the break in the lead caused a fall in its effective output and therefore a significant change in the magnitude of the pacemaker frontal plane vector It is true that this could have been caused by an electronic fault or by almost complete

failure of a battery but such a sudden and large change has never occurred with the Medtronic generators in use. In any event the planned remedial measures by re-operation would have been easier rather than more difficult if the diagnosis had proved to be wrong and the generator had been found to be faulty

Similar arguments can be applied to bipolar epicardial/myocardial systems and to unipolar endocardial and epicardial/myocardial systems. The actual change in the pacemaker frontal plane vector will depend on the relative positions of the electrodes and the location of the fault so no simple general rule can be given as in the case for bipolar catheter electrodes.

More recently interest has grown in detecting smaller changes in the magnitude of the pacemaker frontal plane vector whereas before only gross changes in magnitude were sought. As explained earlier the most frequent cause of impending pacemaker failure is a premature failure of one or more mercury cells. When this occurs, the battery voltage falls and the current output of the pacemaker is reduced. The fall in battery voltage is sometimes accompanied with increased battery internal impedance which reduces the current flow still more. This causes a noticeable reduction in the magnitude of the pacemaker frontal plane vector and if additional cells do not fail, the magnitude of the vector will not change again There is therefore no need for emergency action when this occurs, assuming pacing has not ceased but arrangements should be made for changing the generator on a planned basis in the foreseeable future. If two cells fail there is an even bigger reduction in the size of the vector Incidentally if the vector is unchanged in direction the catheter electrode or the epicardial/myocardial leads system is in perfect order This is useful information to have prior to re operation

The pacemaker frontal plane vector can also be a guide to normal battery rundown There is a tendency to expect generators to fail after a certain time, depending on the literature circulated by manufacturers and one's own experience. The frontal plane vector technique has enabled reassurances to be given that a pacemaker is still functioning perfectly normally Once the battery voltage begins to fall because of normal depletion the voltage will fall steadily over a period of a few weeks and there will be corresponding reductions in the magnitude of the pacemaker frontal plane vector It might be argued that one is not justified in stretching the implanted lifetime of a pacemaker in this way Each case must obviously be judged separately but attempts should be made to extend gradually and carefully the implant lifetimes of pacemakers.

The technique is now undergoing further development in which emphasis will be placed on even greater accuracy A digital measuring unit is currently undergoing trials which if successful will give measurements of greater accuracy Once a series of highly accurate measurements can be obtained they may throw further light on the buildup of fibrous tissue around electrodes

There are also theoretical difficulties which have yet to be resolved For instance in synthesizing the pacemaker frontal plane vector from measurements obtained using Leads I II and III an equilateral triangle or hexaxial system is used which is the basis of conventional electrocardiography and there is some discrepancy between the direction of the vector and that which is expected from the relative positions of the electrodes as shown on the corresponding x ray of the patient's chest.

Nevertheless, in spite of the theoretical difficulties the technique is proving to be of great value in confirming whether a pacemaker is functioning normally or otherwise. It has enabled pacemaker faults to be detected and diagnosed and more recently its use has been extended to detect premature failures of one or two cells. There is every indication that with improved accuracy normal battery depletion will be indicated by a pacemaker frontal plane vector which gradually decreases in magnitude, thus allowing generators to be replaced on a planned basis. Its use is recommended to all those responsible for the care of pacemaker patients whatever type or make of pacemaker has been implanted.

REFERENCES

1 Zoll P M Resuscitation of the heart in ventricular standstill by external cardiac stimulation New Eng J Med 247:768 1952
2 Elmqvist, R. and Senning A. Medical electronics, London 1960 Iliffe and Son p. 253
3 Chardack, W M Gage, A. A. and Greatbatch W A transistorized self-contained implantable pacemaker for the long term correction of complete heart block Surgery 48:643 1960.
4 Advances in Cardiac Pacemakers (Conference Proceedings) Annals of the New York Academy of Sciences, New York, vol 167 article 2 pp 515-1075.
5 Green G. D Forbes, W Bain, W H Shaw G B and Kenmure, A. C F Pacemaker lifetimes—A review and definitions, based on experience in Glasgow with Chardack-Greatbatch (Medtronic) pacemakers, AMER. HEART J In press.
6. Hursen T: Nuclear energy sources. Presented at the New York Academy of Science Conference on Advances in Cardiac Pacemakers, New York, 1968
7 United Kingdom Atomic Energy Authority Isotope-powered cardiac pacemakers, Atom 150 102 1969
8. Silver A. Root, G. Byron, F N and Sandberg H Externally rechargeable cardiac pacemaker Ann. Thorac. Surg 1:380 1965
9 Salkind A. Primary and secondary cells. Presented at New York Academy of Science Conference on Advances in Cardiac Pacemakers, New York November 1968.
10. Siddons, A. H M and Sowton, E. Cardiac pacemakers, Springfield Ill 1968, Charles C Thomas, Publisher
11 Parsonnet, V Gilbert, L. Zucker I R. and Maxim M M Complications of the implanted pacemakers A scheme for determining the cause of the defect and methods of correction J Thorac. Cardiovasc. Surg 45:801 1963
12. Nickel, J Oscilloskopisches verfahren zur unblutigen analyse von uberleitungsstorungen implantierter elektrischer schrittmacher Z. Kreislaufforsch. 53 1149 1964
13. Sowton E. and Davies, J G Investigation of failure of artificial pacing Brit. Med J 1:1470, 1964.
14. Kantrowitz A Implantable cardiac pacemakers, Ann N Y Acad. Sci. 111 1049 1964
15 Knuckey L. McDonald, R. and Sloman E. A method of testing implanted cardiac pacemakers, Brit. Heart J 27 483 1965
16. Dekker E. Büller J and Schuilenburg R. M Aids to electrical diagnosis of pacemaker f ilure, AMER. HEART J 70 739 1965
17 Lillehei, C. W., Cruz, A. B Johnstude, I and Sellers, R. D A new method of assessing the state of charge of implanted cardiac pacemaker batteries, Amer J Cardiol. 16:717 1965.
18. Bluestone, R. H. Harris, A. M Davies, J G Aftercare of artificially paced patients, Brit. Med. J 1 1589 1965.
19 Gordon, A. J: Catheter pacing in complete heart block Techniques and complications, J.A.M.A 193:1091 1965
20 Schaldack, M Buckerl E. S. and Nasserie M Eine methode zuer post operativen uber wachung von patienten m t implantiertem schrittmacher Klin. Wschr 44- :396, 1966.
21 Preston, T A. Judge, R. D Bowers, D L. and Morris, J D Measurement of pacemaker performance AMER. HEART J 71:92 1966.
22 Furman, S. Parker B Escher J and Sch el-del J B Instruments for evaluating function of cardiac pacemakers, Med. Res. Engin. 111:29 1967
23 van den Berg Jw Rodrigo, F A. Thalen, H J Th. and Koops, J Photo-analysis of the condition of implanted pacemakers and electrode circuits (Papers I and II) Prog Roy Neth Acad Sci (Series C) 70: No. 4 1967
24 Stopczyk, M and Pieniak, M Determination of causes of ineffective pacing in patients with implanted fixed rate pacemakers, Pol Med. J VIII: No. 4 1969
25 Moss, A. J and Rivers, R. Myocardial perforation by a permanent transvenous pacemaker New Eng J Med. 275:265 1966.
26. Mower M M Aranga, C. E., and Tabatznik, B Unusual patterns of conduction produced by pacemaker stimuli AMER. HEART J 4:24 1967
27 Meckstroth, C. V Schoenfeld M D and Wardwell, G A. Myocardial perforation from a permanent endocardial electrode J Thorac. Cardiovasc. Surg 51 16, 1967
28. Danielson G. K. Shabetai R. and Bryant L. R Failure of endocardial pacemaker due to late myocardial perforation, J Thorac. Cardiovasc. Surg 51:42 1967
29 Castellanos, A. Maytin, O Lemberg L and Castillo, C. Unusual QRS complexes produced by pacemaker stimuli, AMER. HEART J 77 732, 1969
30. Macfarlane P W and Green, G D Vectorcardiographic studies of implanted cardiac pacemaker stim ll. Presented at the Tenth International Conference on Vectorcardiography in Warsaw October 1969
31 Green G D Forbes, W Bal W H and Shaw G B: Detecting break insulation in negative pacemaker lead Brit. Med. J 4:645 1968.
32 Green G D Forbes, W Bain W H Shaw G. B and Kenmure, A. C. F Detection of faults i implanted cardiac pacemakers, Brit. Heart J 6 707 1969
33 Einthoven, W., Fahr G and deWaart, A. On the direction and ma ifest size of the variations of potential i the huma heart and o the influence of the positio of the heart on the form of the electrocardiogram, AMER. HEART J 40:670, 1955

Clinical communications

Clinical aspects of endomyocardial fibrosis in Bahia, Brazil

Armênio C. Guimarães, M.D.
José P. Esteves, M.D.
Ademar S. Filho, M.D.
Vanise Macedo, M.D.
Bahia, Brasil

In Bahia, an eastern state of Brazil, there are climatic, socioeconomic, and racial similarities to the areas of Africa in which endomyocardial fibrosis is endemic. In this part of Brazil there is also a high prevalence of Chagas' myocarditis, rheumatic heart disease, and portal hypertension due to hepatosplenic schistosomiasis. At present, endomyocardial fibrosis is often confused clinically with these conditions.

The purpose of this paper is to describe the principal clinical, laboratory, electrocardiographic, hemodynamic, radiologic, and angiocardiographic findings in 12 cases of endomyocardial fibrosis studied in Bahia, in order to facilitate proper clinical diagnosis. It is also hoped that these additional cases will help increase our understanding of the distribution and eventually the pathogenesis of the condition.

Subjects and methods

The clinical presentation, routine laboratory data, electrocardiographic, radiologic, angiocardiographic, and hemodynamic findings from 12 patients studied at Hospital Professor Edgard Santos in Bahia, Brazil, and considered to have endomyocardial fibrosis are presented.

Patients ranged in age from 13 to 35 years (mean 25 years). Seven were women. The racial distribution of 1 Negro, 4 Caucasians, and 7 mulattoes reflects the makeup of our local population. All 12 were from the lower socioeconomic groups, but none were grossly malnourished.

Standard 12-lead electrocardiograms (ECG's) were obtained in all patients. Diagnostic criteria were those recommended by the New York Heart Association. Eleven patients had posteroanterior (PA), right anterior oblique (RAO), and left anterior oblique (LAO) chest x-rays.

Eight of these patients died later and the diagnosis was confirmed at autopsy. Paraffin sections of the heart were stained by hematoxylin and eosin, Mallory's blue anilin for connective tissue, Weigert van Gieson's method for both collagen and elastic tissues, Gomori's silver method for reticulum, the periodic acid–Schiff (PAS) method, and Gomori's trichome stain. The criteria for the anatomic diagnosis were the same as used in Uganda by Davies.[3] He

From the Department of Medicine, University of Bahia Medical School, Salvador, Bahia, Brazil.
This work was partially supported by a grant of the Commonwealth Fund.
Received for publication March 16, 1970.
Reprint requests to: Dr. Armênio C. Guimarães, Hospital Professor Edgard Santos, Salvador, Bahia, Brazil.

described a marked fibrous thickening of the endocardium which usually extended into the inner third of the myocardium There was predominant involvement of the ventricular inflow tract with relative sparing of the outflow tract Frequently the fibrous process encased the papillary muscles of both mitral and tricuspid valves. The chordae tendineae were often fixed by the fibrous process and the leaflets were thickened and retracted This more commonly involved the posterior leaflet of the mitral valve

In the 4 patients still alive (Patients 9

Table I Symptoms in endomyocardial fibrosis

Patient No	Age (yr)	Sex	Race	Type of E M F		Dyspnea on exertion	Peripheral edema
				Right ventricular	Biventricular		
1	24	F	Mulatto	+	–	+†	+
2	29	M	Mulatto	+	–	+†	+
3	19	F	Caucasian	+	–	+	+
4	25	M	Mulatto	–	+	+	+
5	26	F	Mulatto	–	+	+†	+
6	27	M	Mulatto	–	+	+	+
7	30	F	Mulatto	–	+	+	+
8	28	F	Caucasian	–	+	+†	+
9	35	F	Caucasian	–	+	+	+
10	13	M	Caucasian	–	+	+	+
11	30	M	Mulatto	–	+	+†	+
12	14	F	Negro	–	+	+	+

Diagnosis confirmed at necropsy
†Initial symptom.

Table II Physical signs in endomyocardial fibrosis

Patient No	Pulse rate	Blood pressure	Cardiac signs					
			Palpable apex impulse	Muffled heart sounds	Fixed split second sound	Loud pulmonary component of the second sound	Third heart sound	Fourth heart sound
1	76	95/65	–	+	–	–	–	–
2†	86	95/70	–	+	–	–	–	–
3	110	100/80	+	–	+	–	–	–
4	80	140/100	+	–	+	–	+	–
5†	75	90/60	–	+	+	–	–	–
6	65	110/85	+	–	–	+	–	–
7	100	130/95	+	+	–	+	–	–
8	120	100/80	–	–	–	–	+	–
9	88	100/70	+	–	+	+	+	+
10	72	100/70	+	+	–	+	+	+
11†	90	120/95	+	+	+	+	+	–
12	81	100/70	–	+	–	+	–	+

Murmurs graded from + to ++++++
†Patient with large chronic pericardial effusion.

to 12) the clinical diagnosis was further supported by angiocardiography and measurement of the pressures of the right side of the heart. The venous angiocardiograms were obtained by the injection of 50 ml. of 75 per cent Diodrast through a catheter whose tip was in the superior vena cava. After 8 to 10 seconds, a PA film was taken. The pressures were measured via a 6F Cournand catheter and a Philips electromanometer and recorded in a Cardiopan 573 heat stylus recorder. The midthorax was used as the zero reference level. The right atrial pressure was measured in all

Ascites	*General weakness*	*Palpitation*	*Right upper quadrant pain*	*Diarrhea*	*Nausea and vomiting*	*Dizziness*	*Cough*	*Fever*
+	+	+	+	+	−	+	−	−
+	+	−	+	+	−	+	+	+
+	+†	+	+	+	−	−	−	+
+	+	−	+	−	+	−	+	+
+	+	+	+	+	+	−	−	−
+	−	+	+	+	+	+†	+	+
+	+	+	−	−	+	+	−	−
+	+	+	−	+	+	−	+	−
+	−	+	+	+	−	+	−	−
+	−	+	−	−	−	−	+	+
+	+	+	−	−	−	+	+	−
+	+	−	+†	+†	+†	−	−	−

		Extracardiac signs							
*Mitral regurgitant murmur**	*Tricuspid regurgitant murmur**	*Distended neck veins*	*Venous abdominal collateral circulation*	*Ascites*	*Hepatomegaly*	*Splenomegaly*	*Peripheral edema*	*Cyanosis*	*Clubbing of the fingers*
−	−	+	+	+	+	+	+	+	+
−	−	+	+	+	+	+	+	−	−
−	++	+	+	+	+	+	+	−	−
++	−	+	+	+	+	+	+	−	−
−	−	+	+	+	+	−	+	+	+
++++	−	+	+	+	+	+	+	+	−
+++	++	+	−	+	+	+	+	−	−
++	−	+	+	+	+	+	+	+	−
+++	++	+	+	+	+	+	−	−	−
+++	+	+	+	+	+	+	−	−	−
++	++	+	−	+	+	+	+	−	−
++	−	+	+	+	+	+	+	−	−

4 patients The right ventricular pressure was obtained only in 2 of them (Patients 9 and 12)

In these same 4 patients right atrial and systemic arterial blood specimens were analyzed for oxyhemoglobin saturation in an anterior oblique (AO) oximeter

Results

Symptoms The symptoms from these 12 patients are tabulated in Table I The 3 major chronic manifestations of the disease were dyspnea on exertion edema and ascites General weakness palpitations and right upper quadrant pain were also very common

Edema and ascites were severe and ascites were progressively refractory Seven of these patients with severe splanchnic congestion had episodes of nausea vomiting and diarrhea Four of them noticed the presence of blood in their stools

Severe dyspnea eventually developed in 6 patients. It was concomitant with the development of a severe degree of ascites in 5 and showed definite improvement after paracentesis. Severe congestive heart failure with dyspnea occurred terminally in the sixth patient Paroxysmal nocturnal dyspnea was a rare event occurring only in Patient 5

In 4 patients an acute episode occurred simultaneously with or preceded by a variable length of time the appearance of these chronic manifestations. Patient 4 had fever for a few days associated with mild to moderate facial and leg edema, which progressed to anasarca Patient 7 had a transient left hemiplegia one year before she first noted shortness of breath Patient 9 had an episode of fever arthralgia and anterior chest pain which increased on inspiration Three years later this patient started to feel strong neck vein pulsations and developed ascites edema and dyspnea on exertion Patient 10 had fever anterior chest pain which increased on inspiration and cough productive of yellow sputum Three days later he suddenly developed right hemiplegia that regressed completely in 2 weeks. Ascites, edema and dyspnea on exertion appeared a few weeks later

Physical signs The most striking physical findings were related to congestion of the right heart circulation All 12 patients had neck vein distension ascites, and a firm enlarged liver Splenomegaly was noted in 11 and 10 had edema. Table II documents that heart rate and blood pressure changes were not striking The apex impulse was not palpable in 5 patients. Of the 9 patients with biventricular endomyocardial fibrosis (E.M F) a loud pulmonic component of the second sound was present in 6 an early diastolic gallop in 5 and an apical pansystolic murmur radiating to the left axilla in 8 In 5 patients a pansystolic murmur at the lower right sternal border was noted to increase on inspiration Cyanosis of the fingers and lips was seen in 4 patients associated with clubbing in 2 of them

Three patients had striking pericardial effusions (Table II) These effusions were chronic and did not produce tamponade. Figs 1 *A* and 2 *A* illustrate 2 of these effusions.

Clinical course The clinical course varied from the acute inexorable illness seen in Patient 4 who died after 6 months to the 13 year survival of Patient 2 (mean of 4 years) An acute onset did not appear to affect the length of illness.

The clinical course was interrupted with sudden rapid deterioration and death in a matter of weeks or months in 2 patients In Patient 3 the initial diagnosis of hepatosplenic schistosomiasis led to splenectomy In the immediate postoperative period he developed fever chest pain that increased on inspiration and frank congestive heart failure He died 2 months later after a downhill course Patient 6 developed an acute lymphangitis of the legs 3 months before death There was progressive deterioration of his cardiac function with terminal hypotension and anuria

Three of the remaining 5 patients died suddenly in the hospital The final 2 had slow continuous deterioration with protracted hypotension and anuria.

Laboratory findings The principal laboratory data is presented in Table III Only 2 patients were anemic. Eosinophilia was a common finding The serum albumin tended to be low and the serum globulin was frequently increased being greater than 4 0 mg per cent in 3 instances. The antistreptolysin-O titer was measured in



Fig. 1. A. PA chest film of Patient 2 showing a huge globular cardiac shadow due to severe pericardial effusion. B. Pericardiectomy markedly diminished the cardiac shadow. Observe the characteristic bulge of the right heart border due to severe dilatation of the right atrium.

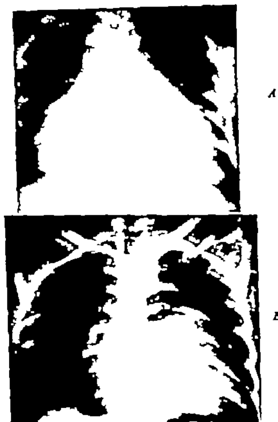


Fig. 2. A. PA chest film of Patient 11 showing a huge globular cardiac shadow due to pericardial effusion. B. Same patient after drainage of the pericardial effusion and injection of air. The cardiac silhouette remains enlarged with prominent bulge of the right border due to right atrial enlargement. The thin parietal pericardium can be seen.

3 patients it was elevated only in Patient 9 who showed an initial titer of 500 Todd units, normal 3 months later. The complement fixation test for *Trypanosoma cruzi* was done in 10 cases, and was positive only in Patient 6. At necropsy the heart of this patient did not show any evidence of Chagas myocarditis.

The 3 patients with severe, chronic, pericardial effusions had this fluid cultured and innoculated into guinea pigs with negative results for *Mycobacterium tuberculosis*. In 2 of these patients this fluid had a chylous appearance, while in the third one, (Patient 11) it was clear.

Electrocardiograms. Normal sinus rhythm was present in 9 patients, associated with frequent VPC's in 4 of them. The P-R interval was longer than 0.20 sec. in 5 of these 9 patients with normal sinus rhythm. Two of them were on digitalis when the ECG was recorded. Three patients were in chronic atrial fibrillation including one with a chronic pericardial effusion.

Five patients had a P wave greater than 0.11 and a prolonged negative phase of P in V_1 and are considered to have shown left atrial enlargement. Fig. 3, B is an example. Only one patient had a peaked P wave in Lead II suggestive of right atrial enlargement.

In 9 patients, the total voltage of the QRS in V_1 ranged from 3.0 to 5.0 mm with a mean of 4 mm. In V_2, it varied from 11.0 to 25.0 mm, mean of 15.0 mm. Fig. 3, B illustrates this point.

Low voltage QRS was present in all leads in 4 cases, and only in the limb leads of 3 others. Two of these former 4 and one of these 3 latter patients had severe peri-

4 patients. The right ventricular pressure was obtained only in 2 of them (Patients 9 and 12)

In these same 4 patients right atrial and systemic arterial blood specimens were analyzed for oxyhemoglobin saturation in an anterior oblique (AO) oximeter

Results

Symptoms The symptoms from these 12 patients are tabulated in Table I The 3 major chronic manifestations of the disease were dyspnea on exertion edema and ascites General weakness palpitations and right upper quadrant pain were also very common

Edema and ascites were severe and ascites were progressively refractory Seven of these patients with severe splanchnic congestion had episodes of nausea vomiting and diarrhea Four of them noticed the *presence of blood in their stools.*

Severe dyspnea eventually developed in 6 patients It was concomitant with the development of a severe degree of ascites in 5 and showed definite improvement after paracentesis Severe congestive heart failure with dyspnea occurred terminally in the sixth patient Paroxysmal nocturnal dyspnea was a rare event occurring only in Patient 5

In 4 patients, an acute episode occurred simultaneously with or preceded by a variable length of time the appearance of these chronic manifestations Patient 4 had fever for a few days associated with mild to moderate facial and leg edema which progressed to anasarca Patient 7 had a transient left hemiplegia one year before she first noted shortness of breath Patient 9 had an episode of fever arthralgia and anterior chest pain which increased on inspiration Three years later this patient started to feel strong neck vein pulsations and developed ascites, edema and dyspnea on exertion Patient 10 had fever anterior chest pain which increased on inspiration and cough productive of yellow sputum Three days later he suddenly developed right hemiplegia that regressed completely in 2 weeks. Ascites edema and dyspnea on exertion appeared a few weeks later

Physical signs The most striking physical findings were related to congestion of the right heart circulation All 12 patients had neck vein distension ascites and a firm enlarged liver Splenomegaly was noted in 11 and 10 had edema. Table II documents that heart rate and blood pressure changes were not striking The apex impulse was not palpable in 5 patients. Of the 9 patients with biventricular endomyocardial fibrosis (E M F) a loud pulmonic component of the second sound was present in 6 an early diastolic gallop in 5 and an apical pansystolic murmur radiating to the left axilla in 8 In 5 patients a pansystolic murmur at the lower right sternal border was noted to increase on inspiration Cyanosis of the fingers and lips was seen in 4 patients associated with clubbing in 2 of them

Three patients had striking pericardial effusions (Table II) These effusions were chronic and did not produce tamponade. Figs. 1 *A* and 2 *A* illustrate 2 of these effusions.

Clinical course The clinical course varied from the acute inexorable illness seen in Patient 4 who died after 6 months to the 13 year survival of Patient 2 (mean of 4 years) An acute onset did not appear to affect the length of illness

The clinical course was interrupted with sudden rapid deterioration and death in a matter of weeks or months in 2 patients In Patient 3 the initial diagnosis of hepatosplenic schistosomiasis led to splenectomy In the immediate postoperative period he developed fever chest pain that increased on inspiration and frank congestive heart failure He died 2 months later after a downhill course Patient 6 developed an acute lymphangitis of the legs 3 months before death There was progressive deterioration of his cardiac function with terminal hypotension and anuria

Three of the remaining 5 patients died suddenly in the hospital The final 2 had slow continuous deterioration with protracted hypotension and anuria

Laboratory findings The principal laboratory data is presented in Table III Only 2 patients were anemic. Eosinophilia was a common finding The serum albumin tended to be low and the serum globulin was frequently increased being greater than 4 0 mg per cent in 3 instances. The antistreptolysin-O titer was measured in

Table IV Serial electrocardiographic changes in endomyocardial fibrosis

Patient #	Date		Rhythm	P R interval	Atrial enlargement*		QRS axis	Low voltage of the QRS	Low voltage QRS in V Normal voltage QRS in V	R/S more than 1 in V	IVCD	ST T wave changes
	Month	Y			RA	LA						
1	Jan.,	1955	AF	−	−	−	+90	+	−	−	−	+
	May	1961	AF	−	−	−	+100	+	−	+	−	+
3	May	1963	NSR	0.17	−	−	+45	+	−	+	−	+
	April,	1960	SA	0.20	−	−	+90	−†	+	+	−	−
7	Dec.,	1962	NSR	0.15	−	−	+60	−	−	−	−	+
	Aug.,	1963	NSR	0.15	−	+	+110	−	+	−	−	+
	July	1964	NSR + PVC's	0.23	−	+	+110	−	+	−	−	+
8	Aug.,	1961	Flutter	−	−	−	+120	+‡	+	−	−	+
	April,	1963	AF	−	−	−	−70	+	−§	−	+	+
11	April	1968	NSR + PVC's	0.15	−	+	+90	+	+	−	−	+
	May	1969	AF	−	−	−	+70	+	+	−	−	+
	July	1969	Atrial flutter	−	−	−	+60	+	+	−	−	+

RA = Right atrium; LA = left atrium; IVCD = Intraventricular conduction defect; AF = atrial fibrillation; NSR = normal sinus rhythm; SA = sinus arrhythmia; PVC = premature ventricular contractions.
*New York Heart Association Criteria Committee.
†After pericardiectomy.
‡Restricted to the limb leads.
§Developed low voltage of the QRS in V

cardial effusions. Right axis deviation (a QRS axis of more than +90 degrees) was present in 3 patients (2 with biventricular disease) and R/S greater than one in V. In 4 Only one of these patients had both abnormalities. In one patient, the amplitude of the $S_V + R_V$ was 38 mm (Patient 9 35 years old) Only Patient 8 developed an intraventricular conduction defect All patients had diffusely abnormal S-T segments and T waves.

Serial ECG s were obtained in 4 patients. The interval between the first and last trace varied from 9 months to 8 years. The main serial changes observed were tabulated in Table IV Fig 3 *A* and *B* illustrates the electrocardiographic evolution of one of these patients.

Hemodynamic findings The mean right atrial pressure was elevated in the 4 patients catheterized. The 3 pressure pulses in Fig 4 all show a deep y descent in the atrial tracing and the right ventricular pressure pulses show an early diastolic dip with a rapid rebound and diastolic plateau. In both instances, the end-diastolic pressure was greater than one third of the systolic pressure[4] Table V gives the hemodynamic data.

Radiologic findings A cardiothoracic ratio of more than 50 per cent was observed in 9 patients. In 3 patients, the enlarged cardiac silhouette was due in part to effusion. Two of these 3 were drained. In one, *Fig 2 B* the heart remained large while in the other Fig 1 *B* a normal outline *returned*

In the PA view the cardiac shadow usually presented a globular aspect, with a characteristic bulge of the right cardiac contour Figs. 1 and 2 *B* This bulge was striking in 11 cases. Eight patients had narrowing of the retrosternal space seen in the RAO *projection*. Posterior displacement of the barium-filled esophagus was present in 8 of 10 patients in this view In the LAO view the posterior border of the cardiac silhouette overshadowed the spine in 10 of 11 patients. Three of these patients had severe pericardial effusions.

The lung fields showed a decreased vasculature in 6 patients. A small pleural effusion was observed in 4 patients.

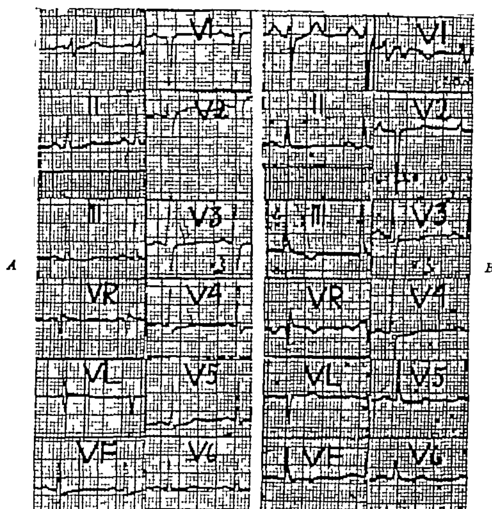


Fig 3 Sequential ECGs from Patient 7 *A* First ECG recorded after one year of congestive heart failure (Dec 17 1962) *B* Thirty two months later (Aug 10 1965) when the duration of the P wave had increased to 0.12 second and a prolonged negative phase developed in \ the QRS axl shifted to the right, and the voltage of the QRS in \ had markedly decreased

Table III *Laboratory data in endomyocardial fibrosis*

Patient No.	Hgb (Gm/100 ml.)	HCT (%)	ESR (mm./hr)	Leukocyte count		Serum proteins (Gm./100 ml.)		Complement fixation test for T cruzi*	Examination of the stools for parasites
				Total	% Eosinophils	Albumin	Globulin		
1	9 0	32	—	4 000	11	2 7	2 9	Negative	Hookworms
2	14 8	49	—	4 500	6	2 8	3 0	—	Ascaris
3	11 9	38	64	7 800	22	4 7	3 0	Negative	S mansoni
4	8 0	26	—	8 300	4	3 1	3 5	—	—
5	11 7	45	—	6 000	8	2 4	4 3	Positive	Ascaris, hookworms
6	13 4	40	—	4 600	6	3 1	4 1	Negative	S. mansoni
7	12 0	48	—	—	—	2 9	3 5	Negative	Ascaris, S. mansoni
8	13 5	50	—	6 000	2	3 5	2 8	Negative	Hookworms, S mansoni
9	10 2	40	4	5 000	3	5 6	2 4	Negative	Ascaris
10	11 7	41	41	5 000	9	4 2	2 2	Negative	Ascaris, S. mansoni
11	12 0	42	50	5 400	14	2 9	5 1	Negative	Hookworms, S. mansoni
12	16 0	53	29	5 000	4	3 1	2 9	Negative	Ascaris

Abbreviations: Hgb = Hemoglobin; HCT = hematocrit; ESR = erythrocyte sedimentation rate.

tissue especially in the subendocardium myocardium.

The predominance of the functional disturbance of the right ventricle in cases of biventricular endomyocardial fibrosis makes the clinical presentation of patients with this form of the disease very similar to those with isolated right ventricular disease (Table I) A very helpful clinical indication of left ventricular EMF is evidence of mitral regurgitation. Eight of our patients presented a mitral regurgitant murmur (Table II) and had posterior displacement of the barium-filled esophagus on the RAO projection. The mechanism of this mitral regurgitation is suggested in Fig 7 which shows the encasement of the left papillary muscles by the fibrous process and adherence of the posterior leaflet of the mitral valve to the posterior wall of the left ventricle. A similar mechanism may operate in the tricuspid valvular apparatus leading to tricuspid regurgitation. Five of our patients presented a tricuspid regurgitant murmur (Table II) Two of them died they showed severe involvement of the right papillary muscles and binding of the septal leaflet of the tricuspid valve against the ventricular septum

Cyanosis and clubbing can occur in both right and biventricular endomyocardial fibrosis (Table II) Its mechanism is still a matter of speculation[7] and warrants further investigation

Laboratory studies are rarely helpful in establishing a diagnosis of endomyocardial fibrosis. Eosinophilia of 6 to 20 per cent is usually present, but is common in our population and is probably related to the high incidence of associated parasitic disease (Table III) Serum albumin tended to be low possibly reflecting the commonly observed cardiac cirrhosis and perhaps due in part to an increased loss of albumin into the gastrointestinal tract.

The electrocardiographic findings were of some help in diagnosing *endomyocardial* fibrosis. Low QRS voltage was present in 7 cases, and in 9 patients the very low voltage of the QRS in V contrasted with the higher voltage of the QRS in V as illustrated in Fig 3 B Tranchesi has considered this abnormality as an electrocardiographic sign of right atrial enlargement. The mechanism by which right atrial enlargement influences ventricular voltage patterns is unclear However the fact that this QRS relationship occurred in 75 per cent of our patients is interesting and a helpful diagnostic clue which certainly warrants further confirmation and explanation.

Fig 3 *A* and *B* shows ECGs recorded 32 months apart to illustrate that in endomyocardial fibrosis the electrocardiographic abnormalities may develop slowly When the first ECG was recorded showing only minor ST T-wave changes, this patient was already in frank congestive heart failure. Thirty two months later there were signs of left atrial enlargement and right axis deviation the QRS complex in V_1 presented a marked decrease in voltage.

One of the most characteristic radiologic features of endomyocardial fibrosis is a bulge of the right cardiac border observed in the PA film.[9] This bulge may be secondary to a pericardial effusion a dilatation of the right atrium or most commonly to both factors.[18] This is very well illustrated by Patients 11 and 12 (Figs. 5 and 6)

In 6 of our patients, the pulmonary vasculature was decreased reflecting the low right ventricular output. This diminution was more marked in the 3 cases with isolated right ventricular disease as can be seen in Fig 1 Only 1 patient with biventricular disease showed a moderate increase in his pulmonary vasculature. This patient was shown postmortem to have severe and predominant left ventricular involvement.

An interesting angiocardiographic finding in Patient 12 was the presence of a filling defect in the right atrial cavity (Fig 6) Such filling defects have been reported by Cockshott[19] and interpreted as a consequence of intra-atrial thrombi Six of our 8 patients who died who did not have angiocardiograms, had a right atrial thrombi at necropsy

Another characteristic angiocardiographic finding in endomyocardial fibrosis is nonvisualization of the apex of the right ventricle,[18] present in Patients 11 and 12, and illustrated in Figs. 5 and 6. Our angiographic and autopsy findings support the view that this nonvisualization is due to obliteration of the cavity by the thick



Fig 7 Postmortem photograph of the left ventricle from Patient 7 The severe endocardial fibrosis encases the papillary muscles and the chordae are shortened and thickened. The posterior leaflet of the mitral valve is fixed against the ventricular wall

The coronary arteries were free from atheroma and no evidence of a diffuse arteritis was found

Organized thrombi were found in the right atria of 6 patients, and in the left ventricular cavity of one Only Patient 2 who had a large ball valve thrombus in his right atrium had a recent pulmonary infarct

Periportal fibrosis consistent with hepatic schistosomiasis was found in 2 of the 8 patients who died (Patients 3 and 6) and documented by a liver biopsy in Patient 10

Discussion

The clinical laboratory electrocardiographic, hemodynamic, radiologic angiocardiographic and pathologic data of our patients suggests to us that endomyocardial fibrosis seen in Bahia is the same disease described by Davies[2] by Shillingford and Somers[4] in Uganda and by Parry and Abrahams[6] in Nigeria.

An acute illness was described in cases of endomyocardial fibrosis by Parry and Abrahams.[6] It was characterized by fever general weakness, and rarely joint pains, and by signs of cardiac involvement including tachycardia out of proportion to the temperature a low pulse pressure and a third heart sound Murmurs of mitral and/or tricuspid regurgitation were heard and pericardial and pleural effusions were present.

Four of our patients had an acute illness with suggestive evidences of carditis. In 2 fever and anterior chest pain which increased on inspiration suggested acute pericarditis Both were later shown to have pericardial effusions In one of these 2 and in a third patient there was a past history of transient hemiplegia These episodes suggested to us an acute endocarditis with mural thrombi in the left ventricular cavity In the fourth patient the presence of fever and facial and leg edema that progressed in a few weeks to severe congestive heart failure was suggestive of an acute carditis

In addition to the description of the acute illness, Parry and Abrahams[6] have also postulated that reactivation of the disease may sometimes occur In 4 of their patients the microscopic findings showed in addition to the fibrosis characteristic of chronic disease areas of granulation tissue increased numbers of lymphocytes mononuclear cells, and pigment laden macrophages. Three of our patients died during an acute phase Patient 4 presented an acute inexorable illness with 6 months duration while Patients 3 and 6 had a stable clinical course interrupted by a sudden and rapid deterioration. In all 3 there was an increased amount of granulation

three cases. In 9 patients the low QRS voltage in V_1 contrasted with the normal voltage of V_6. The chest film of 11 patients showed prominent bulge of the right cardiac border A restrictive pattern was present in the right atrial pressure curve of 4 patients, and in the right ventricular pressure curve of 2.

The main angiocardiographic findings were pericardial effusion and an enlarged right atrium The differential diagnosis in this area includes Chagas myocarditis rheumatic heart disease, and hepatic and pulmonary schistosomiasis. It is hoped that this clinical presentation will lead to increased recognition of the condition in its early stages.

We are grateful to the following: Dr Alvaro Rabello for his help during the hemodynamic studies Dr Fernando Almeida for his help during the angiocardiographic studies Dr Zilton Andrade who made available the illustration of Fig 7; Professor Aluizio Prata, who permitted the inclusion of 2 of his case reports (Patients 3 and 10) and to Dr Sidney J Fillmore (Department of Medicine, Division of Cardiology Cornell University Medical College) whose criticism and encouragement were of fundamental importance in the preparation of this paper

REFERENCES

1 New York Heart Association Criteria Committee: Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis, ed 6, Boston, 1964 Little, Brown & Company p. 418.
2. Davies, J N P Some considerations regarding obscure diseases affecting the mural endocardium, Amer. Heart J 59:600, 1960.
3. Conference Report: Glossary of cardiologic terms related to physical diagnosis and history Third Bethesda Conference of the Committee on Standardized Terminology of the American College of Cardiology and the American Heart Association, Amer J Cardiol. 20:285 1967
4. Yu, P N G., Lovejoy F W Jr Joos, H. A., Nye, R. E., Jr and Mahoney E. B. Right auricular and ventricular pressure patterns in constrictive pericarditis, Circulation 7:102 1953
5. Shillingford, J P and Somers, K.: Clinical and haemodynamic patterns in endomyocardial fibrosis, Brit. Heart J 23 433, 1961.
6. Parry E. H. O and Abrahams, D G. The natural history of endomyocardial fibrosis, Quart. J Med. 34:383, 1965.
7 Abrahams, D G Endomyocardial fibrosis of the right ventricle, Quart. J Med. 31:1 1962.
8. Tranchesi, J Electrocardiograma normal e patológico. Noções de vectocardiografia, ed. 3 S. P ulo, Brazil 1967 Atheneu Editora, p. 130
9 Cockshott, W P Saric, S and Ikeme, A. C. Radiological findings in endomyocardial fibrosis, Circulation 35:913, 1967
10. Cockshott, W P Angiocardiography of endomyocardial fibrosis, Brit. J Radiol 38 192 1965.
11. Laranja, F S., Dias, E., Nobrega, G., and Miranda, A. Chagas disease. A clinical, epidemiologic and pathologic study Circulation 14 1035, 1956.
12. Williams, A. W Ball, J D and Davies, J N P.: Endomyocardial fibrosis in Africa. Its diagnosis, distribution and nature, Trans. Roy Soc. Trop. Med Hyg 48:290, 1954.
13. Crawford, M A. Endomyocardial fibrosis and carcinoidosis. A common denominator? Amer. Heart J 66:273 1963.
14. Shaper A. G., Hutt, M. S. R., Edington, G. M Somers, K., and Fowler J M Endomyocardial fibrosis, Cardiologia 52:20, 1968.

fibrous endocardium Although our findings could be due in part to the single film technique this criticism would not seem to apply to Cockshott's similar findings.

In our hospital population endomyocardial fibrosis can be confused clinically with chronic Chagas myocarditis rheumatic heart disease hepatosplenic schistosomiasis with ascites and tuberculosis pericarditis. In chronic Chagas myocarditis pulmonary and systemic embolic episodes are very common the ECG frequently shows conduction disturbances, especially RBBB with left axis deviation and the complement fixation test for *Trypanosoma cruzi* is positive.[11]

Signs of mitral regurgitation may be present both in patients with biventricular endomyocardial fibrosis and rheumatic heart disease Early development of edema and ascites favor E M F In rheumatic mitral regurgitation a left ventricular heave is usually present, and the ECG usually shows a normal QRS voltage and signs of left ventricular overload

In patients with advanced endomyocardial fibrosis the presence of *Schistosoma mansoni* in the examination of the stools can lead to a diagnosis of hepatosplenic schistosomiasis because the distended neck veins and the heart murmurs are attributed to pulmonary schistosomiasis with chronic cor pulmonale This was the initial diagnosis in 3 of our patients (3 6 and 10) However patients with schistosomal cor pulmonale usually presented a much louder pulmonic component of the second sound and the ECG showed a pattern of right ventricular hypertrophy with strain.

Three of our patients (2 5 and 11) presented a chronic, severe pericardial effusion which also is the common clinical presentation of patients with tuberculosis pericarditis. Against this possibility are the presence of a mitral and/or a tricuspid regurgitant murmur as in Patient 11 (Table II) a thin pericardium (Fig 2 *B*) a characteristic cardiac shadow after pericardial drainage (Figs. 1 and 2 *B*) and the negative results of the bacteriologic study of the pericardial fluid

The final differentiation between any one of these entities and endomyocardial fibrosis can be achieved by the demonstration of the characteristic right angiocardiographic aspects of E M F (Figs 5 and 6) and also by the restrictive pattern shown by the right atrial and ventricular pressure curves of patients with right or biventricular E M F (Fig 4) except for the cases of tuberculous pericarditis

Circumstantial evidence has suggested several etiologies for endomyocardial fibrosis including malnutrition[12] and a heavy ingestion of bananas containing a high content of 5 hydroxytryptamine.[13] The state of nutrition of our patients did not differ from that generally seen in the lower socioeconomic groups. Heavy ingestion of bananas is not a characteristic of this population The parallels between the clinical course of E M F and that of rheumatic heart disease have been recently emphasized by Shaper and co-workers.[14] The clinical aspects of the acute illness observed in 4 of our patients, and those related to the sudden deterioration with death in 2 others, are of interest in this regard However the etiology of endomyocardial fibrosis remains unclear

In summary in Bahia the diagnosis of E.M F should be a leading consideration in a patient who presents signs of acute carditis. This diagnosis should also be considered in cases of chronic edema and ascites with murmurs of mitral and/or tricuspid regurgitation A low voltage of the QRS a bulge of the right cardiac border or a cardiac silhouette suggestive of a large pericardial effusion are additional important diagnostic features. We hope that increased recognition of this disease during life especially in its initial stages, can give clues to a better understanding of this fascinating problem

Summary

The clinical and laboratory findings of 12 patients from Bahia, Brazil with endomyocardial fibrosis are presented All the patients were from the poor socioeconomic group Eight patients who died had necropsy confirmation The disease may present in an acute and chronic form The clinical picture of venous hypertension refractory ascites and peripheral edema was common to all patients at some stage Chronic pericardial effusion was present in

maker senses spontaneous ventricular activation and is suppressed [QRS-blocking] for a period of time determined by the preset rate [escape interval]).[10] Suppression of this pacemaker continues as long as it senses the appearance of a spontaneous QRS potential occurring before the escape interval of the pacemaker has elapsed. This characteristic of the QRS-blocking demand pacemaker may be utilized to test the sensing mechanism and to reveal the underlying rhythm since low amplitude stimuli applied to the chest wall are sensed by the pacemaker.

A technique of chest wall stimulation (CWS) has been previously described.[11] Briefly a regular succession of electrical impulses, produced by a battery powered portable pacemaker are delivered to the anterior aspect of the chest wall through two suction electrodes applied to the skin and connected by alligator clips to the positive and negative poles of the external unit. Using electrolyte paste or jelly to reduce skin resistance, the suction cups are initially applied to the skin of the chest in the position of the conventional precordial electrocardiographic electrodes V_1 and V. A control electrocardiographic tracing is obtained before CWS is started. With the ECG running CWS is begun at a rate slightly higher than the rate of the patient's implanted pacemaker at a current of 3 Ma. The rate and amperage of the portable pacer and the position of the suction cups are adjusted until complete suppression of the implanted pacemaker is obtained. In most cases suppression of the implanted pacemaker is immediate. Occasionally however the position of the suction cups needs to be changed several times about the lower parasternal and precordial areas before effective suppression is accomplished. A rhythm strip or a complete electrocardiogram may then be obtained. If the patient's underlying rhythm is considered dangerous, CWS is terminated immediately by turning off the external pacer. Most patients do not feel the chest wall impulses unless a current greater than 12 Ma. is utilized. The procedure is well tolerated and no discomfort or cardiac extrasystoles produced by CWS have been noted.

Implantation of the permanent pacemaker was carried out in one patient with third degree heart block and syncopal episodes following a myocardial infarction and in two patients with an unstable sinus-node mechanism who required one or more cardiac drugs.[12] The fourth patient had progressive disease of the conduction system manifested when first seen by partial bilateral bundle branch block and eventual 2:1 A-V block which caused syncope.

Case reports

Case 1. A 68-year-old woman had permanent demand pacemaker implanted for complete heart block with Stokes-Adams syndrome following a myocardial infarction. Prior to the development of complete heart block, she had episodes of severe sinus bradycardia and sinoatrial block.

A of Fig. 1 is control rhythm strip. Group beating is immediately identified on this tracing. Paced beats occur at a rate of 74 per minute, frequently interrupted by intrinsic beats of two different contours. Retrograde conduction from the paced beats to the atrium is evidenced by inverted P waves deforming the T of the paced beats. Retrograde activation of the atrium is followed by beats showing varying degrees of aberrant ventricular conduction. The origin of these beats cannot be accurately determined. Although they appear to be related to the artificial pacemaker activity it is difficult to distinguish them from ectopic ventricular beats. A possible Wenckebach sequence in the retrograde direction exists between the paced beats and the atrial response. In addition, there is a second possible Wenckebach sequence in the antegrade direction with 3:2 response between the inverted P waves and the beats which follow them. The varying morphology of these beats suggests a third possible Wenckebach mechanism of the left bundle branch or alternatively that these are premature ventricular contractions from several different foci.

In *B* CWS at rate of 135 per minute produces complete suppression of the pacemaker and the underlying rhythm is then disclosed. Group beating and retrograde conduction are again identified. The rhythm is junctional with 3:2 Wenckebach response in the antegrade direction, probably between the A-V junction and the bundle of His, and a 3:2 Mobitz type block in the retrograde direction. The time of retrograde conduction between the junctional tissues and the atrium in the first conducted beat of each group is 0.28 sec. It should be noted that the retrograde conduction time in the second conducted beat is only 0.21 sec. probably due to facilitated transmission of the impulse to the atrium during the supernormal period of excitability of the upper junctional tissues. The shorter retrograde conduction time of the second beat of each group, and the progressively delayed antegrade conduction, cause the second atrial depolarization to appear earlier in the T wave and produce shortening of the R-P interval.

Chest-wall stimulation A method of demand QRS blocking pacemaker suppression in the study of arrhythmias

Alfonso J Trevino M.D
Barry M Beller M.D
Robert C Talley M.D
Giovanni A Pupillo M.D
Joseph W Linhart M D
San Antonio Texas

Demand pacemakers are now widely used in the treatment of various arrhythmias.[1-4] Despite relative inexperience with their use they are felt to offer certain advantages over fixed rate units Among these are the potentially longer battery life of QRS-blocking pacemakers in certain standby applications and the absence of competitive rhythms sometimes seen with fixed rate pacing [5] Although attempts have been made to make these devices insensitive to external electrical signals the permanent demand pacemaker may still be subject to interference with its function by such stimuli Interference is produced by nondiscriminatory sensing by the pulse-blocking or detection circuit.[6,7] QRS synchronous units respond to such stimuli by increasing their rate up to a fixed limit [8] or by reverting to a fixed rate function [7] whereas the QRS-blocking pacemaker is suppressed when it senses external stimuli at a rate faster than its preset rate.[9] By applying low amplitude electrical stimuli to the chest wall at a rate sufficient to suppress the QRS-blocking pacemaker one may obtain information about the intrinsic rhythm of the heart with only temporary interference with pacing [9] We have found this technique to be useful in the study of progressive disease of the conduction system and of pacemaker conduction system interaction without interference with optimal patient therapy It is the purpose of this communication to demonstrate these applications of the technique through illustrative cases.

Material and methods

All of the electrocardiograms were recorded in the pacemaker clinic of the Bexar County Teaching Hospital from patients with permanently implanted demand QRS-blocking pacemakers (Medtronic Model 5841) paced through a transvenous endocardial electrode catheter (Medtronic Model 5816) in contact with right ventricular endocardium (This pace-

From the Section of Cardiovascular Disease, Department of Physiology and Medicine University of Texas Medical School at San Antonio, and the Bexar County Hospital, San Antonio, Texas.
Received for publication March 16, 1970.
Reprint requests to Barry M. Beller M D University of Texas Medical School at San Antonio, 7703 Floyd Curl Drive, San Antonio, Texas 78229

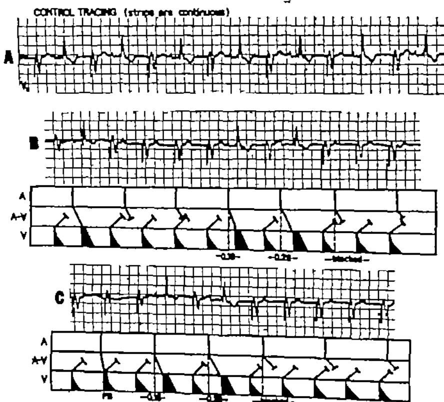


Fig. 2. Electrocardiograms obtained from Case 2. *A*, *B*, and *C* are continuous tracings obtained prior to CWS. Paced beats are identified as well as intrinsic beats originating in the atria with apparent second degree A-V block of the Wenckebach type. The Wenckebach periods are clearly shown in the ladder diagrams which accompany *B* and *C*. See text for detailed explanation.

bach type P-R prolongation occurs in the conducted beats, without immediately apparent cause, and a similar phenomenon is recognized in *C*, which also shows a fusion beat (second beat). From these electrocardiograms, it is impossible to determine whether this phenomenon occurs because of the development of spontaneous second degree A-V block or because of concealed penetration of the A-V junction by the pacemaker stimuli.

The electrocardiogram in Fig. 3, recorded during CWS at 135 to 150 beats per minute, reveals the mechanism of progressive P-R prolongation to be most likely due to concealed, retrograde penetration of the junctional tissue by the pacemaker stimuli. When the pacemaker is suppressed by CWS, this phenomenon disappears. In *A* and *B*, the rhythm is identified as sinus bradycardia at 50 beats per minute with P-R interval 0.15 sec. and QRS aberration of the right bundle branch block type. In *C*, A-V block is not produced even when carotid sinus massage is performed during CWS.

Case 3. A 67-year-old woman developed pressure necrosis and secondary infection of the skin of the anterior chest wall at the site of a previously implanted QRS-blocking demand pacemaker. The indication for permanent pacing in this patient was sensitivity to digitalis needed for control of congestive heart failure secondary to coronary heart disease. While on digoxin, 0.125 mg. daily, she had frequently developed sinus bradycardia, sinoatrial block, atrial flutter, and atrial fibrillation with worsening congestive heart failure, symptoms of cerebral ischemia and azotemia. At the time of admission for pacemaker revision, a diagnosis of bacterial endocarditis was made on the basis of fever, leukocytosis, hemolytic anemia, and splenomegaly. Multiple blood cultures were negative, probably as a result of previous antibiotic therapy. It was decided to remove the entire pacemaker unit because it represented the focus of infection. The question was raised, however, as to whether or not a temporary pacemaker should be inserted transvenously as a safety measure during the period of treatment of endocarditis. A logical objection to this procedure was that the temporary pacemaker catheter might also serve as a continuing focus of infection. The dilemma was solved by CWS as shown in Fig. 4, which revealed atrial fibrillation with an adequate ventricular rate of 64 per minute. Thus, the infected unit was removed and a temporary

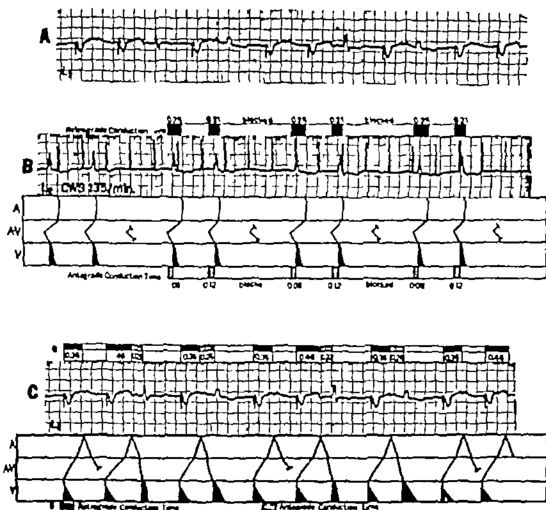


Fig 1 Representative electrocardiographic tracings from Case 1 A is a rhythm strip prior to chest wall stimulation (CWS) Paced beats and intrinsic beats of two different contours are identified B is taken during CWS and reveals intrinsic beats of a single contour occurring irregularly The accompanying ladder diagram provides a possible explanation for this intrinsic rhythm C is a reproduction of A with an explanatory ladder diagram, using information obtained during CWS See text for full explanation

The demonstration of antegrade and retrograde second degree block resulting in group beating without bizarre beats of varying left bundle branch block contour clarifies the mechanism of the arrhythmia. In C the original electrocardiogram shown in A is reproduced with an explanatory ladder diagram. It can be seen that the original sequence was produced by retrograde conduction in which the Wenckebach phenomenon is demonstrated in successive retrograde atrial depolarizations. This is evidenced by calculated retrograde conduction intervals which show lengthening Note that retrograde conduction times can only be analyzed when repetitive pacemaker discharges occur A retrograde atrial depolarization is not seen when a reciprocal beat occurs within the standby period of the pacemaker thereby suppressing its discharge. After each reciprocal beat a new cycle begins An antegrade Wenckebach phenomenon is seen with each of the retrograde P waves. It is possible to determine that these are 3:2 Wenckebach cycles since the demand pacemaker fires more than 0.30 sec. after the third P wave in each group. The rule of Wenckebach indicates that the conduction time from the last P wave to the ventricle should have been 0.30 sec or less. The contour of the reciprocal beats changes, probably because of varying degrees of aberrant conduction through the left bundle branch

Case 2 A 56-year-old woman had a permanent demand pacemaker implanted because of an unreliable sinus rhythm. Arrhythmias prior to pacemaker implantation included atrial flutter and paroxysmal atrial tachycardia. When digitalis was given in small doses for attempted control of the rapid arrhythmias, a severe sinus bradycardia with ventricular premature contractions occurred Fig 2 shows representative strips of Lead V recorded in the pacemaker clinic as part of the routine follow up evaluation. In A a bigeminal rhythm produced by paced beats alternating with conducted sinus beats is seen. The conducted beats fall 50 msec. before the next expected pacemaker stimulus and suppress the QRS-blocking demand pacemaker In B what appears to be an instance of progressive Wencke-

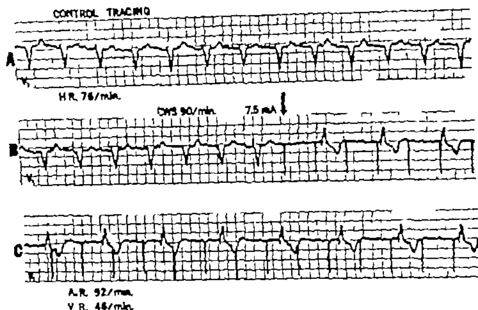


Fig. 5. Representative electrocardiographic tracings in Case 4 obtained Sept. 9, 1969. *A*, taken prior to CWS, reveals a paced rate of 76 per minute; no intrinsic beats are noted. In *B* and *C*, taken during CWS, the underlying rhythm would appear to be sinus with 2:1 A-V block and complete right bundle branch block.

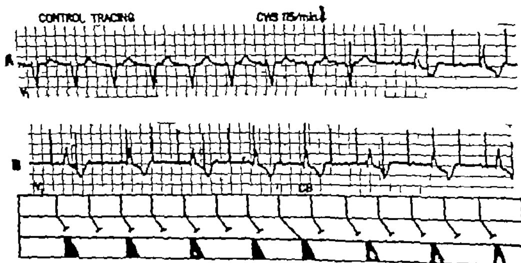


Fig. 6. Representative electrocardiographic tracing in Case 4 obtained Oct. 14, 1969. *A* reveals the onset of CWS which is continued through *B*. Again, no intrinsic beats are noted prior to CWS. During CWS, the ventricular rate is 46 with apparent A-V dissociation. In *B* a capture beat (*CB*) is present. See text for details.

C, CWS was applied and revealed apparent 2:1 A-V block with prolonged P-R interval of the conducted beats as well as right bundle branch block configuration of the QRS complexes. The ventricular rate was 46 per minute. On October 14 another follow-up examination was made. At that time, the pacemaker continued to function well, as is revealed by the control tracing shown in *A* of Fig. 6. In *B* recorded during CWS, it is obvious that nearly complete heart block with a rare captured beat (labelled CB) is present. The capture may be to supernormal phase of A-V conduction. It is of interest that the R-R intervals during CWS on September 9 and October 14 are exactly the same, suggesting that

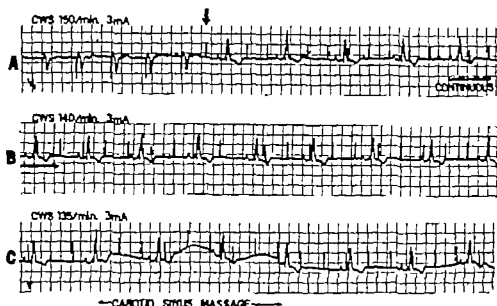


Fig 3 Electrocardiogram obtained from Case during CWS. *A* and *B* are continuous. In the absence of paced beats no A V block is apparent. *C* taken during CWS and carotid sinus massage again reveals no A V block. See text for details.

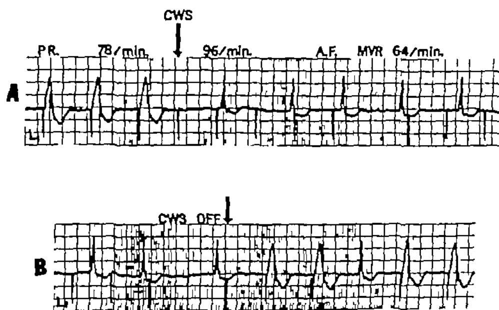


Fig 4 *A* nd *B* are electrocardiogram from Case 3 showing the onset and termination of CWS. In the bsence of CWS the intrinsic rhythm is impossible to ascertain. However once CWS i begun atrial fibrillation at a rate of 64 per mi ute is identified

pacemaker was not inserted. The patient did well on strict bed rest, salt restriction and antibiotics. After six weeks a new permanent unit was implanted without incident. Approximately two months later the patient died of acute myocardial infarction. Autopsy also revealed a healed abscess of the mitral valve annulus.

Case 4 A 68-year-old man with first degree heart block associated with small Q waves in Leads I and aV_L, left axis deviation, and right bundle branch block for several years has been followed in our cli ic. In March, 1969 he developed syncope associated with documented 2 1 atrioventricular block and a ventricular rate of 30 per minute. A permanent, QRS-blocking demand pacemaker was inserted at that time nd he did well thereafter

At routine follow-up on Sept. 9 1969 CWS was performed The results of this procedure are shown in Fig 5 In *A* the control tracing, regularly paced rhythm at 76 beats per mi ute is present. In *B* and

the patient's diseased conduction system and the implanted pacemaker. A puzzling instance of progressive second degree block without immediately apparent cause was clarified by suppression of artificial pacemaker activity induced by CWS. With the pacemaker temporarily suppressed, the patient was noted to have sinus bradycardia with 1:1 A-V conduction, indicating that A-V block had not developed spontaneously but was induced by concealed penetration of junctional tissue by pacer stimuli. Thus, the possible erroneous impression of A-V junctional conduction abnormalities developing in a patient who had previously had only sinus-node disease was prevented.

The value of CWS in reaching a decision as to whether a patient with subacute bacterial endocarditis needed temporary pacing after removal of an infected permanent pacemaker is illustrated by our Case 3. CWS revealed that despite the previous occurrence of severe bradyarrhythmia, the patient had an adequate ventricular rate at the time of planned removal of the infected permanent pacemaker. Insertion of a temporary pacing catheter during the period of uncontrolled infection was unnecessary, and the potential hazard of persisting infection due to a temporary catheter pacemaker was eliminated.

The fourth case described herein is instructive in that the performance of CWS on several follow-up visits has allowed us to accurately assess the course of a patient with progressive disease of the conduction system. This patient had left anterior hemiblock and complete right bundle branch block for several years before the development of symptomatic 2:1 A-V block which required the insertion of a demand pacemaker. On all of his follow-up visits, no spontaneous activity has been seen without pacemaker suppression induced by CWS. Therefore, without application of this technique no follow-up data concerning the conduction system would be available. The use of CWS six months after insertion of the permanent demand pacemaker revealed apparent 2:1 A-V block, whereas repeat CWS one month later revealed nearly complete heart block with a definite idioventricular rhythm. It was noted that the R-R intervals on tracings performed on these two occasions were exactly the same, suggesting that complete heart block was already present on the first follow-up examination. The use of CWS has allowed us to confirm the development of complete heart block from bilateral bundle branch disease.

The ease of application and safety of this technique have prompted us to use CWS as a routine part of the follow-up of patients with implanted demand pacemakers of all types. CWS provides not only an opportunity to determine the type of pacemaker and test its function, as has been described by others,[13,14] but also allows us the opportunity to gather follow-up information about the conduction system of each patient with a QRS-blocking demand pacemaker that would be otherwise unobtainable.

Summary

Low amplitude electrical stimuli delivered to the chest wall from a portable pacemaker may be used to suppress the implanted QRS-blocking demand-type pacemaker. This technique allows analysis of the underlying electrocardiogram. The value of this method in the study of the natural history of conduction system disease, pacemaker-conduction system interaction, and in management of patients wearing these devices is illustrated.

REFERENCES

1. Furman, S., Escher, D. J. W., and Solomon, N.: Standby pacing for multiple cardiac arrhythmias, Ann. Thorac. Surg. 3:327, 1967.
2. Ryan, G., Easley, R., Jr., Zaroff, L., and Goldstein, S.: Paradoxical use of a demand pacemaker in treatment of supraventricular tachycardia due to Wolff-Parkinson-White syndrome. Observations on termination of reciprocal rhythm, Circulation 38:1037, 1968.
3. Lemberg, L., Castellanos, A., and Berkovits, B. V.: Pacemaking on demand in AV block, J.A.M.A. 191:12, 1965.
4. Hornbaker, J. H., Jr., Humphries, J. O., and Ross, R. S.: Permanent pacing in the absence of heart block: An approach to the management of intractable arrhythmias, Circulation 39:189, 1969.
5. Zuckerman, W., Zaroff, L. I., Berkovits, B. V., Matloff, J. M., and Harken, D. E.: Clinical experiences with a new implantable demand pacemaker, Amer. J. Cardiol. 20:232, 1967.

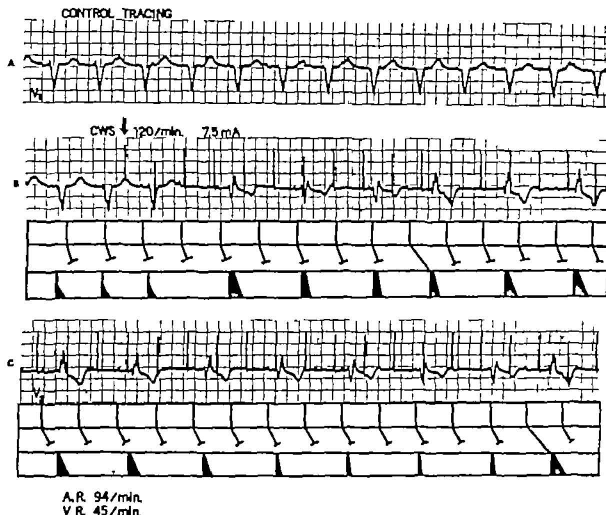


Fig. 7. Representative electrocardiographic tracings in Case 4 obtained Nov. 11, 1969. *A*, taken prior to CWS stimulation, reveals a paced rate of 76 per minute; no intrinsic beats are identified. *B* and *C* are continuous tracings taken during CWS. Again, A-V dissociation is present with varying degrees of ventricular aberration. It is postulated that the aberration is secondary to intermittent partial conduction of right bundle branch. See text for details.

complete heart block with an "in step" phenomenon may have been present in September. Fig. 7, obtained at the most recent follow-up examination, performed on November 11, shows the pacemaker functioning well (*A*). Chest wall stimulation illustrated in *B* and *C* reveals that nearly complete heart block is still present and associated with varying degrees of ventricular aberration. This finding is believed to be due to intermittent partial conduction in the right bundle branch.

Discussion

The four patients presented here illustrate the use of CWS both for the study of the pathophysiology of the conduction system and to direct therapy in patients with implanted demand (QRS-blocking) pacemakers. In the first case CWS disclosed the mechanism of an interesting arrhythmia accompanying pacemaker activity to be reciprocal beating induced by pacemaker activity and complicated by second degree block in the antegrade and retrograde directions. The presence of Wenckebach periods in the antegrade direction and Mobitz periods in the retrograde direction evident during CWS confirms the presence of this type of conduction disturbance as the cause of the varying R-P intervals and dropped reciprocal beats present when the pacemaker is functional. It strongly suggests that a similar mechanism is responsible for the varying morphology of the reciprocal beats, and that they are conducted rather than premature ventricular contractions.

Case 2 illustrates interaction between

A new pharmacologic phonocardiography by the use of angiotensin

Hiroshi Yamamoto, M.D.
Kikuo Arakawa, M.D.
Tsutomu Yamashita, M.D.
*Hiroaki Murakami, M.D.**
*Teruo Sakai, M.D.**
*Shinichiro Torii, M.D.***
*Motoomi Nakamura, M.D.***
Kitakyushu and Fukuoka, Japan

Since most of the valvular heart diseases are now listed as the curable or potentially curable forms of heart disease, a precise diagnosis by auscultation has become much more important in medical practice. One of the most useful diagnostic devices thus developed has been the pharmacologic method in phonocardiographic diagnosis.

Of the many drugs studied for this purpose since the study by Wiggers, amyl nitrite[2] and methoxamine[3] have become generally accepted. The former is helpful in differentiating right-sided heart murmurs, e.g., pulmonary stenosis from ventricular septal defect or tetralogy of Fallot, whereas the latter is used for the differential diagnosis of left heart murmurs. Methoxamine is one of the sympathomimetic drugs and is reportedly superior to others such as phenylephrine, norepinephrine, mephenterine, and metaraminol because of its isolated effect on systemic circulation. It is our experience, however, that methoxamine quite often results in untoward side effects, such as headache, chest oppression, gooseflesh reflex, pollakisuria, and sometimes even premature beat or atrioventricular block. Furthermore, these effects usually persist for an unnecessarily long period of time. This is nothing to be wondered about if one remembers that methoxamine was so specifically designed and introduced as to meet the need of prolonged sympathomimetic action for various uses. This happens to be rather troublesome for phonocardiography. A better drug which performs the

From the Kitakyushu Kosei Nenkin Hospital, Kitakyushu, Japan, and the Research Institute of Angiocardiology and Cardiovascular Clinic, Kyushu University School of Medicine, Fukuoka, Japan.
This work was supported in part by the Asahi Scientific Award.
Presented before the 33rd annual meeting of the Japanese Society of Circulation at Tokyo on March 28, 1969.
Received for publication March 18, 1970.
Reprint requests to: Dr. Kikuo Arakawa, Associate Professor, Kyushu University School of Medicine, 1276 Katakasu, Fukuoka, Japan.
*Kitakyushu Kosei Nenkin Hospital, Kitakyushu, Japan.
**Research Institute of Angiocardiology and Cardiovascular Clinic, Kyushu University School of Medicine, Fukuoka, Japan.

Vol. 81, No. 1, pp. 29-37 January, 1971

6. Castellanos, A Jr Lemberg L. and Jude, J R. Depression of artificial pacemakers by extraneous impulses, AMER. HEART J 73:24 1967
7. Furman S Parker B Krauthamer M and Escher D J W The influence of electromagnetic environment on the performance of artificial cardiac pacemakers, Ann. Thorac. Surg 6:90 1968
8. Dreifus, L. S. Morse D Watanabe Y and Flores, D The advantages of demand over fixed rate pacing Report of clinical experience Dis. Chest 54:86 1968
9. Furman S. Escher D J W Parker B and Solomon N Electronic analysis for pacemaker failure, Ann Thorac. Surg 8:57 1969
10. Chardack W M Technical information bulletin for Chardack-Greatbatch demand pacemaker Model 5841 Medtronic Inc., Minneapolis, Minn.
11. Smyth N P D Bacos, J M and Keller J W: Progress in cardiovascular surgery Experimental and clinical use of a variable parameter cardiac pacer Dis. Chest 53:93 1968.
12. Abelman, A G and Wigle E. D The brady cardia tachycardia asystole syndrome. Treatment by a pacemaker Canad Med. Ass. J 100:75 1969
13. Samet, P Hildner F Schoenfeld C and Narula O: Effect of chest wall stimulation on cardiac pacemaker function Circulation 40:III 1969 (Abst.)
14. Samet P Center S., Linhart, J W and Keller J W Selected aspects of cardiac pacing Electrocardiographic patterns, Amer J Cardiol. 23:702 1969

Table III Number of changes in heart sounds and murmurs by angiotensin II

Heart sounds and murmurs	Increased	Slightly increased	Not changed	Slightly decreased	Decreased	Total
Heart sound						
First sound	8 (2)	15 (4)	40 (8)	12 (2)	2 (0)	77
Second sound						
Aortic	5 (2)	31 (7)	24 (4)	3 (0)	0 (0)	63
Pulmonic	0	2 (1)	7 (1)	2 (1)	0	11
Third sound	5	11 (6)	14 (6)	1 (1)	1	32
Fourth sound	3 (1)	10 (4)	13 (3)	2	0	28
Opening snap						
Mitral	0	11	7	0	0	18
Tricuspid	0	0	1	1	0	2
Heart murmur						
Functional systolic murmur	0	1	7	1	0	9
Ejection systolic murmur						
Aortic	0	0	2	0	0	2
Pulmonic	2	3	13	2	1	21
Regurgitant systolic murmur						
Mitral	3	2	3	0	0	8
Shunt						
Patent ductus arteriosus	5	0	0	0	0	5
Ventricular septal defect	4	1	2	0	0	7
Blowing diastolic murmur (aortic insufficiency)	3	0	0	0	0	3
Rumbling diastolic murmur	1	2	2	1	0	6

Angiotensin II (0 075 μg per kilogram injected in 30 sec.)
( ) Normal subjects.

Table III there was striking enhancement of diastolic regurgitant murmur in aortic insufficiency (Fig 4) and systolic murmur in ventricular septal defect (Fig 5) as well as in continuous murmur in patent ductus arteriosus (Fig 6) Mitral regurgitant murmur was enhanced (Fig 2) in 5 out of 8 cases. The 3 patients who remained unchanged were either in heart failure or complicated with secondary tricuspid incompetence due to mitral stenosis.

Ejection-type systolic murmur was also enhanced in tetralogy of Fallot, but this was not found to be the case with pulmonary stenosis (Fig 7)

No significant change was observed in functional murmur

Discussion

Information about the cardiovascular effects of angiotensin has been sufficiently accumulated by many investigators. It is now well known that angiotensin is the most potent pressor substance ever known and this is mostly due to the vasoconstrictive action especially in small arteries. On the other hand as in the case of methoxamine or phenylephrine it has no significant effect in the pulmonary circulatory bed These pharmacologic characteristics resembling methoxamine should provide as good a pharmacologic change as methoxamine or phenylephrine do which is needed in phonocardiography It worked exactly as it should and furthermore angiotensin showed even more advantages than methoxamine in that, being a natural metabolite it has no serious side effects and if there are any they cease to exist in just a few minutes as they are quickly inactivated in the body Biological half-life of angiotensin is a matter of minutes.

Intensification of the murmurs, as seen in patent ductus arteriosus ventricular septal defect, tetralogy of Fallot mitral insufficiency and aortic insufficiency is conceivably due to the increase of the pressure difference between systemic and pulmonary circulatory systems.

Fig 2 The accentuation of the third heart sound and the opening snap as well as the regurgitant murmur by angiotensin njection in a patient with mitr l stenoinsufficiency Registered from top to bottom, by 35 70 140 (24 db) 250 and 140 (18 db) H *SM* = Systolic murmur *B P* = blood pressure *OS* = opening snap.

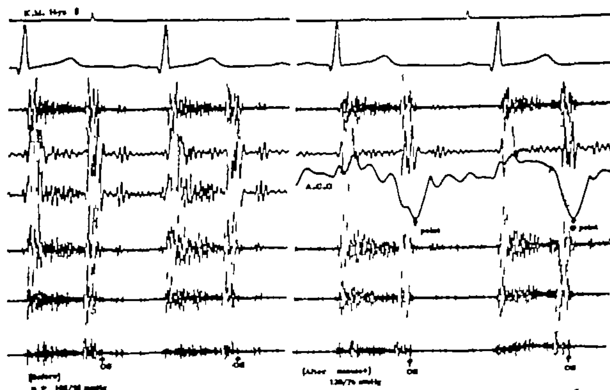


Fig 3 The accentuation of the open ng snap by angiotensi I jection I patient with mitral stenoinsufficiency The opening snap, as is evidenced by the association with O poi t in pexcardiogram (*A C.G*) is definitely enhanced in ampl tude after the administration of angiotensin. Registered by 140 (18 db.) 35 70 140 (24 db) 250 and 400 Hz.

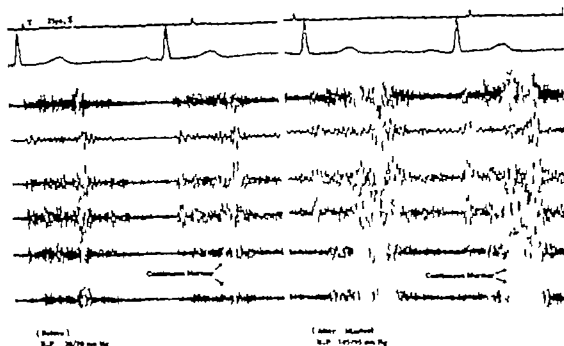


Fig. 6 The increment of continuous murmur by angiotensin injection in patient with patent ductus arteriosus (*PDA*). For the band pass, see Fig. 3.

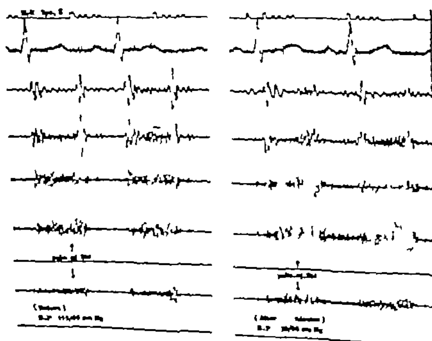


Fig. 7 The increment of pulmonic ejection systolic murmur by angiotensin injection in a patient with Fallot tetralogy. For the band pass, see Fig. 2.

Fig 4 The increment of blowing diastolic murmur (*DM*) and accentuation of II component by angiotensin injection in a patient with aortic insufficiency For the band pass, see Fig 3.

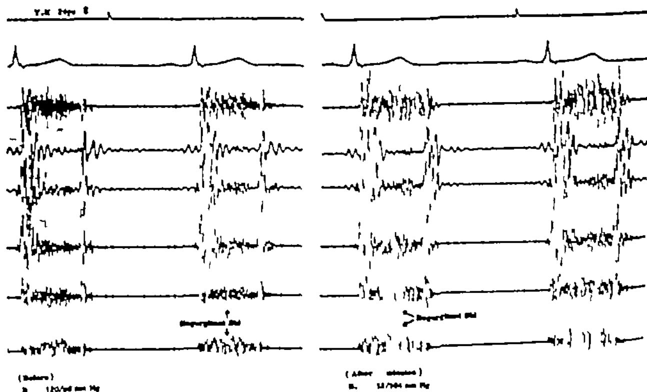


Fig 5 The increment of regurgitant systolic murmur by angiotensin injection in a patient with ventricular septal defect (*VSD*) For the band pass, see Fig 3

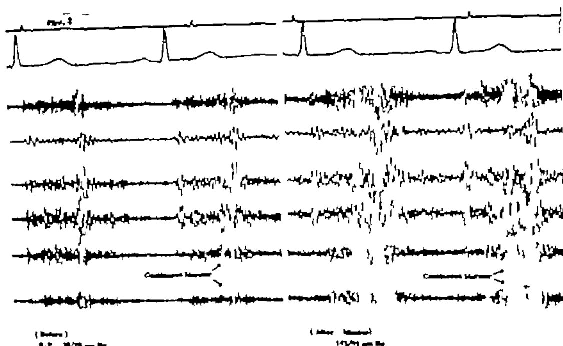


Fig. 6 The increment of continuous murmur by angiotensin injection in a patient with patent ductus arteriosus (*PDA*). For the band pass, see Fig. 3.

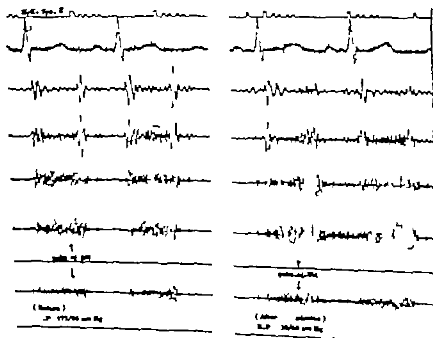


Fig. 7 The increment of pulmonic ejection systolic murmur by angiotensin injection in patient with Fallot' tetralogy. For the band pass, see Fig. 2.

Fig 4 The increment of blowi g diastolic murmur (*DM*) and accentuation of II component by angiotensin injection in a patient with aortic insufficiency For the band pass see Fig 3

Fig 5 The increment of regurgitant systolic m rmur by angiotensin injection in a patient with ventricular septal defect (*VSD*) For the band pass, see Fig 3

12. Rodin, P and Tabatznik, B Effect of change of posture on added heart sounds, Circulation 21:1022, 1961 (Abst.)
13. Ueda, H., Sakamoto, T Uozumi, Z., Inoue K., Kawai, N and Yamada, T The use of methoxamine as a diagnostic aid in clinical phonocardiography Jap Heart J 7:204 1966.
14. Tavel, M E., Frazier W J and Fisch, C Use of phenylephrine in the detection of the opening snap of mitral stenosis, AMER. HEART J 77:274 1969
15. Ueda, H Sakamoto, T Uozumi, Z Kobayashi, T Kawai, N Yamada, T Inoue, K., Ichinose, S Watanabe, H., and Kaito, G. Clinical advantage of the use of amylnitrit in functional phonocardiography Jap. Arch. Intern. Med. 12:951 1965 (in Japanese)
16. Heeg E., and Meng, K.: Die Wirkung des Bradykinins, Angiotensins und Vasopressins auf Vorhof Papillarmuskel und isoliert durchströmte Herzpräparate des Meerschweinchens, Arch. Exp. Path. Pharmakol. 200:35 1965

That pulmonary-systolic ejection murmur was intensified with angiotensin in 2 out of 21 cases (Table III and Fig 7) seems somewhat contradictory but both cases were tetralogy of Fallot and this has been a well known characteristic also with methoxamine or phenylephrine [11] Since this is opposite to what is expected in simple pulmonary stenosis angiotensin may serve to differentiate the former from the latter

Mitral opening snap which is the hall mark in diagnosing mitral stenosis, is sometimes difficult to detect As shown in Figs. 2 and 3 however angiotensin did intensify the opening snap and even made it detectable this had been unrecognizable before the administration of angiotensin Trial of an intensification of the opening snap has been hitherto unsuccessful except for amyl nitrite despite many other trials i e by the change of respiration or body position[12] and use of methoxamine[13] or phenylephrine [14] Only inhalation of amyl nitrite[13] was reported to accentuate mitral opening snap but it was also accompanied by tachycardia and shortening of the II -opening snap interval both interfering with the detection of the opening snap Angiotensin intensified it without any significant change in the II -opening snap interval and heart rate indicating the usefulness of angiotensin as a new device in detecting the mitral opening snap The mechanism was not systematically investigated here but the most probable factor in the possibilities may be the increased pressure gradient between the left atrium and ventricle in early diastole due to the mild positive inotropic action of angiotensin to ventricular myocardium A weak positive inotropic action of angiotensin on the atrium was reported in animals.[16]

There was no significant untoward effect except for a slight chest oppression in a few cases but angiotensin should be used with particular care in cases of coronary sclerotic or myocardial diseases.

Summary

A potent vasoconstrictive action and the hemodynamic consequences of angiotensin selective to the systemic circulatory system were applied in functional phonocardiography in place of methoxamine or phenylephrine As with methoxamine or phenylephrine, regurgitant murmurs occurring in the left heart increased significantly with angiotensin while right sided heart murmurs remained unchanged

Angiotensin however is much more advantageous than methoxamine because of the much sharper action of only a few minutes duration without any untoward effect, making it useful even in the out patient clinic.

Furthermore angiotensin intensified the mitral opening snap in several cases of mitral valve failure not significantly affecting the II -opening snap interval and the heart rate and is indicated to be useful as a new device for detecting opening snap

REFERENCES

1 Wiggers, C. J Factors determining the relative intensity of the heart sounds in different auscultation areas, Arch. Intern. Med (Chicago) 21:471 1919
2 Kahler H Über das verhalten der Herzgeräusche bei Einwirkung von Amylnitrite Wien Arch. Innere. Med. 23:349 1933
3 Goodman L. S. and Gilman A. The pharmacological basis of therapeutics, New York 1960, The Macmillan Company
4 Page I H and Bumpus, F M Angiotensin Physiol Rev 41:331 1961
5 Arakawa K., Nakatani, M Minohara, A. and Nakamura, M Isolation and amino acid composition of human angiotensin I Biochem. J 104:900 1967
6. Arakawa, K. Minohara A. Yamada, J and Nakamura, M Enzymatic degradation and electrophoresis of human angiotensin I Biochim. Biophys. Acta 168:106 1968.
7 Aoyagi H. Arakawa, K. and Izumiya N Synthesis of human angiotensin I J Amer Chem. Soc. 89:4239 1967
8. Page, I H and McCubbin J W Renal hypertension Chicago 1968, Year Book Medical Publishers, Inc.
9 Rose J C. Kot, P A. Cohn, J N Freis, E. D and Eckert G E. Comparison of effects of angiotensin and norepinephrine on pulmonary circulation, systemic arteries and veins, and systemic vascular capacity in the dog *Circulation* 25:247 1962
10. Khairallah P K. Page I H Bumpus, F M., and Smeby R. R.: Angiotensin II: Its metabolic fate Science 138:523 1962.
11 Vogelpoel L. Schrire, V., Nellen M and Swanepoel A. The use of phenylephrine in the differentiation of Fallot's tetralogy from pulmonary stenosis with intact ventricular septum, Amer. Heart J 59:489 1960.

Table I Age at time of diagnosis and sex distribution of patients with S-A block

Age	*30*	*31-40*	*41 50*	*51-60*	*61 70*	*70*	*Total*
Women		4		6	3		13
Men	1	1	2	1	2	1	8
							21

Table II Subclassification of patients with S-A block

Type	*N block*	*Syncopal attacks*
Second degree	11	8
Alternating second undetectable sinus activity	10	7
Total	21	15

*The classification is based solely on the available ECG recordings.

the exclusion of slow atrial fibrillation. Figs. 1 2, and 3 show representative ECG tracings from 3 of these 10 patients. In analogy with the single A V nodal beat in second degree S-A block, the more permanent nodal rhythm functioned as the common escape rhythm during absence of sinus activity The nodal beats occurred without atrial capture or with P waves before within or after the QRS complexes, or varied between these forms. Six patients showed in periods a nodal bigeminy fulfilling the criteria of reciprocal beats or rhythm[4] (Fig 1 and Table III)

S-A block with Wenckebach periodicity was not observed

Fifteen patients experienced Stokes-Adams attacks (Table II) Several others had spells of dizziness without loss of consciousness. ECG was recorded during or immediately after an attack in 11 patients in all showing isolated nodal beats and no sinus activity or long pauses of second degree S-A block. In the 4 remaining patients other conditions, such as transitory A V block, might have been responsible but this seems improbable. Ventricular asystole did in no case precede the S-A block during the attacks. No patient died in asystole but several needed vigorous resuscitation. Severe brain damage ensued in 2 patients. Thus, Stokes-Adams attacks in S-A block are not rare and may be almost as malignant as in A V block.

As all the recorded attacks occurred during increasing S-A block there is reason to believe that all 15 patients actually had undetectable sinus activity during their syncopes. Thus, as many as 18 patients may have had this arrhythmia for periods.

Other symptoms seemed largely unrelated to the S-A block. Three patients had anginal chest pain and congestive heart failure was present in the patients with coexistent valvular heart disease. Bradycardia clearly aggravated these symptoms in some patients.

The etiology of the arrhythmia was in most cases obscure. Several patients, however had previously had infectious or systemic diseases of possible etiological significance (Table IV) In no case was digitalis or other drugs found to be of main etiological importance, but one patient with previous S-A block deteriorated after digitalis medication. In two other cases digitalis could not be ruled out as a contributory factor but discontinuing the drug did in no case eliminate the block. Likewise there was no evidence from the histories of disease that increase of vagal tone precipitated or worsened the symptoms in any patient. No relationship could be demonstrated between the fluctuations of the disease and serum electrolytes, which were normal in all patients.

The recorded additional disturbances of impulse formation and conduction were multiple (Table III) Of particular interest

Chronic sinoatrial heart block

Knut Rasmussen M D
Oslo Norway

Since the introduction of cardiac pace makers most interest has been focused on atrioventricular (A V) block while less attention has been paid to sinoatrial (S-A) block The latter has been considered a rare and transient disturbance of rhythm seldom giving rise to severe symptoms.[1] In Norway however S-A block constitutes about ten per cent of the rhythm disorders requiring permanent artificial pacing [2]

This report describes 21 patients with second degree S-A block It shows that S-A block may be a serious and chronic condition which frequently gives rise to escape rhythms and tachycardias of various origins and in which pacemaker therapy is often necessary The alternation between bradycardia and tachycardia creates specific diagnostic and therapeutic problems.

Material and methods

The 21 patients reported were seen at the department from 1966 to 1968 All patients with clinically significant S-A block have been included while patients with nonsignificant block dominant ectopic activity or major A V block have been excluded Care was taken to avoid false diagnosis of S-A block in the presence of premature nonconducted P waves [3]

All patients were examined by routine 12 lead electrocardiograms (ECG's) Esophageal lead recordings were performed in cases of doubt concerning the existence or localization of P waves. Some patients with rapidly fluctuating rhythms were monitored in an intensive ward until the diagnosis could be established

The diagnosis of S-A block was made according to the criteria of Greenwood and Finkelstein [4] A second degree S-A block has been diagnosed when the pauses between the P waves were exactly a multiple of the basic P P distance or deviated less than 0 10 sec. from this. Previous reports have not always applied precise criteria with respect to this deviation [4]

Results

Almost two thirds of the patients were women Eight were below the age of fifty when the ECG diagnosis was first made (Table I)

In 11 cases the only kind of S-A block recorded was the classical fluctuation between second degree S-A block and sinus rhythm (Table II) In the remaining 10 patients sinus rhythm with second degree S-A block was interrupted by shorter or longer periods of undetectable sinus activity During these periods all the 10 patients showed a consistent A V nodal rhythm usually at a rate of about 40 per min and no sinus-induced P waves were found even with esophageal leads. Retrograde P waves were found in most cases, contributing to

From the Medical Department B., University Hospital, Rikshospitalet, Oslo, Norway
Received for publication March 31 1970.
Reprint requests Dr Knut Rasmussen, Medical Department B., University Hospital, Rikshospitalet, Oslo, Norway

is the great tendency toward various tachycardias and escape rhythms. In some patients only isolated beats of atrial, nodal or ventricular origin occurred in the S-A block pauses. Fourteen patients, however had attacks of atrial tachycardias. In these patients the heart rhythm fluctuated between bradycardia and rapid supraventricular rhythms, either of which could be dominant. The episodes of tachycardia could last from an hour to several months.

In one case the transition from sinus rhythm with intermittent S-A block to atrial fibrillation was recorded (Fig. 4). After a pause of 1.4 sec, atrial fibrillation ensues with the next A-V nodal beat.

The group has been observed for a total of 143 patient-years, from the time the diagnosis was made to the time of insertion of a pacemaker or to April, 1969. The observation period varied from a few days, when pacing was urgent, to 23 years, with an average of 7 years. Sixteen patients were observed without a pacemaker for more than one year, 11 for more than 4 years, and 6 for more than 10 years.

Generally the stability of the arrhythmia has been remarkable, with uniform electrocardiographic pictures for several years. In only two cases have episodes of significant S-A block been followed by stable normal rhythm.

Only one patient died during the observation period. She had suffered from diphtheria 6 years earlier and had during her last years, an alternating rhythm with second degree S-A block, first degree A-V block, and paroxysmal, and later permanent atrial fibrillation. Electroconversion of her atrial fibrillation was carried out and sinus rhythm restored with periods of nodal rhythm and S-A block. Two days after the electroconversion she had a cerebral embolus and died. Atrial fibrillation recurred before death. At autopsy, microscopic sections showed extensive fibrosis of the sinus

Table III. Additional disturbances of rhythm in 21 patients with S-A block

Rhythmic disturbances	No. of patients
Conduction defects:	
A-V block I (PQ ≧ 0.22)	3
II	1
Left bundle branch block	1
Escape rhythms and tachycardias:	
Single atrial escape beats	4
Single nodal escape beats	21
Single ventricular beats	3
Premature atrial beats	3
Atrial tachycardia	5
Atrial flutter	8
Atrial fibrillation	6
No. of patients with atrial tachycardias	14
Non-bigeminal nodal rhythm	10
Reciprocal nodal rhythm†	3
Reciprocal nodal beats	3
Escape-capture bigeminy	4
Nodal bigeminy unknown type	2
No. of patients with nodal bigeminy	11
No. of patients with stable nodal rhythm	10
Ventricular tachycardia	1

*As several patients had more than one arrhythmia in each group, the number of patients in the groups is smaller than the sum of individuals with each rhythm.

†The reciprocal nodal rhythms have been classified according to the spatial orientation of the P waves in the frontal plane.

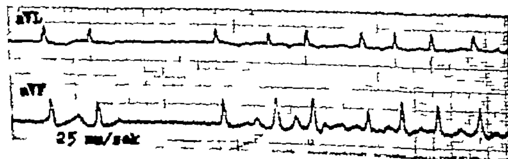


Fig. 4. Atrial fibrillation arising after pause of 1.4 sec. caused by S-A block.

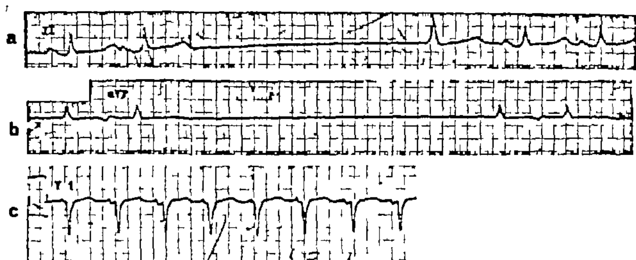


Fig 1 a b and c Electrocardiogram (ECG) tracings from Patient M E. at different times during her disease. a Sinus rhythm with second degree S-A block and 4 dropped sinu beat one nodal escape beat and a pause of 2 3 sec b Period with pure nodal rhythm in this case a table reciprocal rhythm with negative P waves sandwiched between two nodal beats. No spontaneous I waves c Supraventricular tachycardia frequency 160 per m ute.

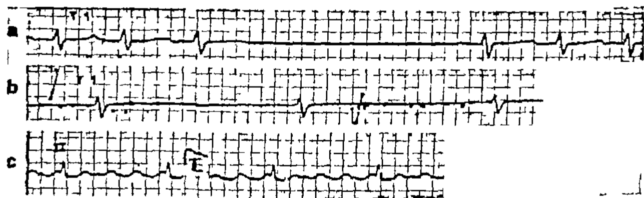


Fig 2 a b and c ECG tracings from Patient S. M A at d fferent t mes a Second degree S-A block with 3 dropped beats, no escape beat nd a pause of 2 2 sec. b Nodal rhythm without detectable P waves, frequency 40 per min te c Atrial fl tter w th 4 1 A V conduction.

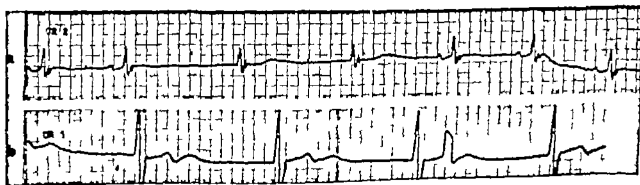


Fig 3 a and b ECG tracings from Patient H S. at different times. a Second degree S-A block with 3 dropped sinus beats and 2 nodal escape beats. b Nodal hythm without detectable P waves, frequency 48 per minute.

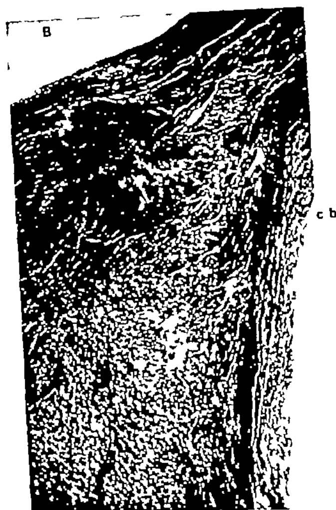


Fig 5B Right: Upper ventricular septum with common A-V bundle (*c.b.*). Elastin stain. Extensive fibrosis within and around the bundle.

node, sinoatrial junction, and ventricular septum within and around the common bundle (Fig 5)

Two patients suffered cerebral anoxic damage during cardiac standstill. Before they had tolerated the S-A block well for 13 and 16 years, respectively The malignant nature of their disease could not be anticipated from the course up to these attacks.

In most patients, drugs have been tried in attempts to maintain normal sinus rhythm or at least a more rapid escape rhythm Isoprenaline given intravenously was effective during acute attacks on several occasions, but was ineffective perorally The best drug was atropine, given intramuscularly under ECG supervision, and if effective, continued by the oral route. Atropine, when effective, accelerated the previously dominant focus, but did not re-establish sinus rhythm. In two cases, atropine seemed to prevent attacks of bradycardia for years.

The 14 patients with alternating brady and tachycardia represented the most difficult therapeutic problem in the group. Drug treatment of the tachyarrhythmias implied risk of induction or aggravation of bradycardias, and the reverse was also possible No drugs could therefore be given over longer periods without possible harmful



Fig. 5A Left S-A node with S-A nodal artery endocardium left-downward and epicardium right-upward Elastin stain. Diffuse fibrosis of the node w th normal artery

Table IV *Additional diseases in 21 patients with S A block**

Disease	*No of patients*	*Previous diphtheria*	*Appearance of S-A block†*
Diphtheria	6	–	17 to 48 yr after average 30 yr
Hepatitis	4	1	Nonrelated
Influenza 1918	3	2	Several years after
Pleurodynia	1	0	12 yr after
Encephalitis	2	0	One immediately after One 10 yr after
Thyrotoxicosis, treated	3	0	Nonrelated
Hypothyroidism, treated	1	0	Nonrelated
M tral stenosis	1	0	Several years after
Mitral stenosis and aortic insufficiency	1	0	Several years after
Aortic insufficiency	1	0	Several years after
Primary myocardial disease	1	0	Several years after
Myocardial infarction	2	1	Before

*The diseases are listed without regard to their possible importance; several patients are, therefore, represented ith more than one additional disease.

†Before = S-A block started before the disease. After = S-A block started after the disease.

did not occur Nevertheless, 2 of the ECG tracings in his report show a probable S-A block.

Recently Sandöe and Flensted Jensen[12] have reported 6 similar cases, 5 of which had S-A block. Of these 5 patients 4 had bouts with supraventricular and 2 with ventricular tachycardias. All patients had Stokes-Adams seizures and were treated with pacemakers, and 3 required beta receptor blocking agents in addition in order to suppress the tachycardia effectively

With these exceptions, this material differs from previous reports on chronic arrhythmias and S-A block. Most readily it may be compared with the extensive material compiled by Greenwood and Finkelstein.[4] They collected 219 patients with S-A block reported during a 30 year period from different parts of the world and added 4 of their own. Two thirds of the reported patients were men 41 had rheumatic heart disease, but only in 7 is previous diphtheria mentioned. Eight patients had atrial fibrillation not much more than would be expected from mere coincidence The material includes several examples of influence from drugs and nervous reflexes in 25 patients digitalis was considered the cause of the S-A block. Only in 7 cases was the duration of the block reported to exceed one year

Some similarities may also be found between the two materials. In both several examples of thyroid disease cerebral disease previous hepatitis, and severe influenza are found, but the numbers are too small to document any systematic relationship.

Etiology Recently Scherf[13] has discussed the mechanisms involved in S-A block. He maintains that because such a block is difficult to produce in animal experiments and because of the numerous junctional fibers between the sinus node and the atrium abnormal conduction alone does not explain the phenomenon. He suggests atrial nonresponsiveness due to subthreshold sinus impulses as a possible mechanism

The data presented here is not directly relevant to this question of electrophysiology But the chronic nature of the block makes it likely that organic lesions within and around the sinus node giving rise to conductional disturbances are the underlying cause. Because of the differences in anatomy however the organic lesions must probably be much more extensive in the sinus node region than in the A V node in order to produce block. This may account for some of the differences in frequency between the two types of block.

As stated by Greenwood and Finkelstein[4] the S-A node may be involved in any pathological process which affects the heart. The organic basis of the chronic S-A block syndrome will therefore be multiple. Rheumatic heart disease was rarely present in this material, but the incidence of previous diphtheria seems remarkably high. According to the diphtheria statistics, almost 130 000 peopl have had clinical diphtheria in Norway after 1916.[14] *Regrettably* information concerning the age distribution of the patients *is not* available in the statistics, so the exact probability of a chance concurrence cannot be found. Nevertheless, it seems probable that diphtheric myocarditis *has* induced a chronic slowly propagating fibrosis in the S-A node and adjacent tissue (Fig 5) which finally has produced the block.

This view is not supported by hospital follow-up studies of patients with previous diphtheria. Thompson, Golden and White[15] did not find S-A block in 100 patients who had diphtheria 15 to 20 years earlier Hoel and Holst Berg[16] selected, from a total of 1 477 patients with diphtheria, 263 with probable heart affection and followed them for 5 to 8 years. They found some conductional defects but not S-A block. The reason for this discrepancy probably is the low incidence of the chronic S-A block syndrome and the long latency period for its development.

Other arrhythmias. In spite of the primary exclusion of major A V block, several patients with conductional defects in the A V node or bundle branches were found This illustrates that the anatomical lesions, whatever their cause, may occupy all parts of the conduction system. The dominant block may arise in any part of the system. The new term "panconductional defect" seems appropriate for this situation. In general, a simultaneous defect of automa

effects This especially applied to digitalis glycosides which ordinarily are the drugs of choice in rapid supraventricular rhythms. In the treatment of tachycardias we have therefore purposely deviated to the tachycardial side.

Seventeen patients were treated with permanent transvenous pacing with electrodes to the right ventricle Ten have at present a demand pacemaker of the QRS triggered type 5 with stable bradycardia have fixed rate units and in 2 the pacemakers have been removed after 10 days and several months of pacing Up to April 1969 the total pacing period was 228 patient months. The pacing has been uncomplicated and attacks of asystole have been completely avoided Some patients who showed frequent parasystolic beats with fixed rate pacemakers have received demand units at battery change

Some of the cases of supraventricular tachycardia were suppressed by establishing a minimal frequency through pacing without the additional use of drugs. In others the addition of digitalis preparations was required In all 14 patients this regime controlled both tachycardia and bradycardia satisfactorily

Discussion

Diagnostic criteria As pointed out by Greenwood and Finkelstein[4] the definition and subclassification of S-A block involves some difficulties. First degree S-A block is clinically undetectable. In second degree S-A block the main diagnostic problem is the differentiation of advanced sinus bradycardia and sinus arrhythmia Slow sinus bradycardia cannot be separated from a constant 2 1 S-A block and the diagnosis of S-A block is only justified if sequences with doubled atrial rate can be recorded Because the pauses in S-A block often are somewhat shorter than the basic P P distance an exact borderline toward advanced sinus arrhythmia cannot always be drawn The limit used here with the acceptance of P P distances down to 0 10 sec. less than the multiple is comparatively rigid However such a limit ought to be included in a precise definition of S-A block.

When no sinus activity can be demonstrated by ECG various mechanisms may be involved the most important of which are true sinus arrest, third degree S-A block and atrial arrest with sinoventricular conduction The latter is a rare occurrence and is excluded in most patients in this study by the finding of retrograde P waves. The question is whether undetectable sinus activity should be classified as third degree S-A block or as sinus arrest.[4] This problem cannot be solved until a method for recording sinus activity in patients is available probably both mechanisms may be operative However the present demonstration of the transition of a second degree S-A block to undetectable sinus activity in at least 10 cases heavily supports the view that a third degree block has developed in these patients and that the relationship between second and third degree block in the S-A node often is quite analogous to that in the A V node Until sinus node ECG recordings are possible it seems reasonable to classify most patients without detectable sinus activity together with patients with definite S-A block

Sampling factors Our hospital is a reference hospital for cardiac patients from the whole country Patients are evaluated for surgical treatment of congenital or acquired heart disease and patients with unusual features or arrhythmias unresponsive to standard treatment will have a high probability of admission Conversely coronary heart disease and transient disturbances of rhythm in the course of acute myocardial infarctions are under represented These factors explain why so many instances of this syndrome have been found in this department. The true frequency in the general population cannot be estimated from this selected material

Previous reports Isolated patients with sustained S-A block and supraventricular tachycardias have previously been reported[7-10] In addition 2 patient materials with similar features have been published Short[11] has described the syndrome of alternating bradycardia and tachycardia in 4 patients 3 of whom had valvular heart disease and none of whom had experienced diphtheria All 4 patients had syncopes and the course of disease was chronic. Short classifies the bradycardia as sinus bradycardia and specifically states that S-A block

their main problem may need a pacemaker as well.

In conclusion this material represents an important group of patients, previously often unrecognized S-A block must be accepted as a potentially chronic and severe dysrhythmia with characteristic clinical features. *Pacemaker treatment is often* required.

Summary

Twenty-one patients with clinically severe second degree S-A block were studied. Six patients had had severe diphtheria 17 to 48 years before. Rheumatic heart disease transitory vagotonia electrolyte disturbances, and drugs were not found to be of main etiological importance. Organic damage of the sinus node and adjacent tissues sometimes caused by diphtheric myocarditis, is the most probable underlying cause.

The S-A block was permanent in most cases and its predominant manifestation was fluctuations of rhythm On one hand 10 patients had periods in which no sinus activity could be demonstrated which may be interpreted as development from second to third degree S-A block. On the other hand, 14 patients had attacks of supraventricular tachycardias, probably representing escape tachycardias caused by sinus impulse failure. The changes in rhythm constituted the dominant therapeutic problem.

The prognosis in S-A block is better than *in A V block, but 15 of the patients had* malignant syncopes and 2 patients had subsequent cerebral damage. The treatment of choice is insertion of a pacemaker which prevents the bradycardia and therefore, also the tachycardia and permits adequate use of digitalis preparations. Seventeen patients had pacemakers implanted, most of them of the QRS-triggered type.

REFERENCES

1. Müller O F and Finkelstein, D Adams-Stokes syndrome due to sinoatrial block, Amer J Cardiol. 17:433, 1966.
2. Storstein, O Treatment of heart block from clinical viewpoint, Acta Med. Scand. 183:557 1968.
3. McGarry T F Sino-atrial block and mechanism of atrial asystole, *I* Dreifus, L. S., Likoff W and Moyer J H., editors. Mechanism and therapy of cardiac arrhythmias, New York, 1966, Grune & Stratton, Inc., p. 125.
4. Greenwood, R. J and Finkelstein, D Sinoatrial heart block, Springfield Ill., 1964 Charles C Thomas, Publisher
5. Scherf D and Cohen, J The atrioventricular node and selected cardiac arrhythmias, New York, 1964 Grune & Stratton, Inc.
6. Tosa, N and Scott, K. W.: Stokes-Adams attacks with simultaneous auricular and ventricular standstill, Circulation 9:833 1954.
7. Cohen, H. E., Kahn, M., and Donoso, E.: Treatment of supraventricular tachycardias with catheter and permanent pacemakers, Amer J Cardiol. 20 735, 1967
8. Cheng, T O Transvenous ventricular pacing in the treatment of paroxysmal atrial tachyarrhythmias alternating with sinus bradycardia and standstill, Amer J Cardiol. 22:874 1968.
9. Birchfield R. I Menefee, E. E., and Bryant, G. D N Disease of the sinoatrial node associated with bradycardia, asystole, syncope and paroxysmal atrial fibrillation Circulation 16:20, 1957
10. Sanghvi, L. M., Unusual cardiac arrhythmias in myocardial infarction. A case with S-A block, paroxysmal A-V nodal tachycardia with varying 2 1 and 3 1 block, dissociation between pacemakers situated within the conduction system nd premature beats in A V rhythm and A V dissociation, Amer J Cardiol. 8 147 1961
11. Short, D S. The syndrome of alternating bradycardia and tachycardia, Brit, Heart J 16:208, 1954.
12. Sandöe, E., and Flensted-Jensen, E. Adams-Stokes seizures in patients ith attacks of both tachy- and bradycardia, a therapeutical challenge, Acta Med. Scand. 186 111, 1969
13. Scherf D. The mechanism of sinoatrial block, Amer J Cardiol. 23 769 1969
14. Statistical Central Bureau, Norway
15. Thompson, W P Golden S. E., and White, P D: *The heart fifteen to twenty years after severe diphtheria*, Amer. Heart J 13:534 1937
16. Hoel, J and Holst Berg, A.: Persistent diphtheric heart disorders, Acta Med. Scand. 145:393 1953.
17. Scherf D., Blumenfeld, S and Yildiz, M.: Experimental studies on A V nodal rhythm following suppression of activity of the sinus node, Amer J Cardiol. 10:234 1962.
18. James T N Myocardial infarction and trial rhythmias, Circulation 24 761 1961.
19. James, T N nd Hershey E. A.: Experimental studies on the pathogenesis of atrial arrhythmias in myocardial infarction, Amer Heart J 63:196, 1962.
20. Hudson, R. E. B The human pacemaker and its pathology Brit. Heart J 22:153, 1960.
21. Johansson, B W.. Complete heart block: A clinical, hemodynamic and pharmacological study in patients with and without an artificial pacemaker Acta Med. Scand. 180:451 1966. (Suppl.)

ticity and/or conductivity in other parts of the heart is probably necessary for an S-A block to give rise to clinical symptoms. Otherwise lower pacemakers should be able to take over before the full block pauses have elapsed [17]

The most characteristic feature of this material is the high frequency of rapid supraventricular tachycardias *Two explanations* may be given for this concurrence First the underlying condition may stimulate atrial automaticity in addition to the producing of S-A block Second the tachycardias may function as escape rhythms induced by the pauses This explanation *seems to be the most probable in most* instances The mechanism has been discussed by James [18] who found necrosis of the sinus node in 11 patients with atrial fibrillation in the course of an acute myocardial infarction Other patients had necrosis of the node without arrhythmias *James, therefore maintains that additional* stimulating factors must be present in order to produce atrial fibrillation In animal experiments damage of the sinus node with additional stimulation with drugs or of the vagal nerve gave a high incidence of supraventricular escape tachycardias [19] *Fundamentally this is the same as the well* known relationship between A V block and ventricular tachycardias. The diagnostic rule is the same in both situations When tachycardia is present suspect the block and when block is present expect tachycardias. With the above mentioned excep*tions however the significance of this* relationship on the supraventricular level has been insufficiently recognized The observation of immediate transition from S-A block to atrial fibrillation (Fig 4) gives additional support to this concept of escape rhythms

This gives rise to the question of how frequently this mechanism causes permanent atrial fibrillation The question has been studied anatomically by Hudson [20] who found sinus node damage in 15 of 65 hearts 14 of which had been in atrial fibrillation Clinically the problem may be approached by studying the disturbances of rhythm after electroconversion of chronic atrial fibrillation In our own material of 437 consecutive conversions 3 patients acquired a nodal rhythm of more than a few *minutes duration Two of them re*verted to atrial flutter within a few days, while the third obtained a stable nodal rhythm Thus S-A block and sick sinus syndrome seems usually to give rise to paroxysmal and not permanent atrial tachycardias

Prognosis Untreated or medically treated chronic S-A block has a definitely better prognosis than A V block where the one year mortality rate on medical treatment is about 40 per cent.[21] In some cases the diagnosis of S-A block has almost no therapeutic or prognostic consequences. On the *other hand the prognosis in our material* has been more serious than is usually observed in S-A block The high frequency of syncope and 2 patients with brain damage show that S-A block as A V block, is a potentially life-threatening disease. Equally important is the fact that major Stokes-*Adams attacks may occur after long periods* with an apparently benign course.

Treatment As described drugs seem to be of little benefit in the control of this chronic condition Any drug regime for bradycardia may increase the frequency and duration of the tachycardial attacks. Likewise *the treatment of the tachycardias* with digitalis or even quinidine may precipitate Stokes-Adams seizures.

It is the authors opinion that the most effective treatment in most of these patients is insertion of a permanent pacemaker preferably of the demand type. In the few *patients with constant bradycardia* a fixed rate unit may do as well P-synchronous pacemakers of course *should not be used* but atrial pacing may be preferable to the ventricular pacing used in our patients. The abolition of atrial tachycardias by pacemaker alone may be considered as an overdrive analogous to the recently introduced pacemaker treatment of ventricular tachycardias, and supports the idea of bradycardia causing tachycardia. After insertion of the *pacemaker antiarrhythmic* drugs may be used without danger

As for A V block pacemaker insertion is indicated after one syncopal attack Anginal chest pain or congestive heart failure aggravated by bradycardia are additional indications. Some patients with tachycardia as

myocardial infarction were reviewed. From this group 21 patients with clear-cut autopsy and clinical evidence of previous myocardial infarction(s) were selected. The hospital records for the initial myocardial infarction and all subsequent hospitalizations, as well as the final hospital course resulting in death, were carefully reviewed. The electrocardiograms were interpreted without knowledge of the clinical or pathological findings. Criteria for ECG diagnosis of infarction were the same as those used in a study previously reported by Dayton and associates.[4] The autopsy reports for each patient were reviewed and the location of healed as well as acute infarcts determined. ECG's taken prior to the final episode showed evidence in each case of the previous myocardial infarction corresponding to areas of fibrosis reported at autopsy. Interpretations of ECG's taken during the period

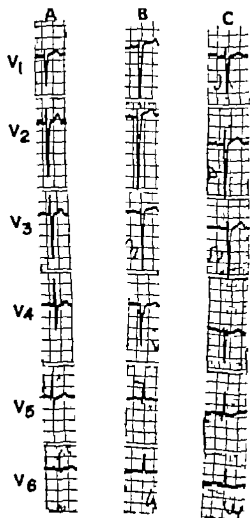


Fig. 1. Patient 9. Chest leads of July 29, 1958 (*A*) preceded the first infarct and are normal. The tracing of Feb. 13, 1963 (*B*) was taken after his initial anteroseptal infarct. The final tracing (C) was taken 11 days before death (April 8, 1963) and shows little evidence of the acute anterolateral infarct found at autopsy.

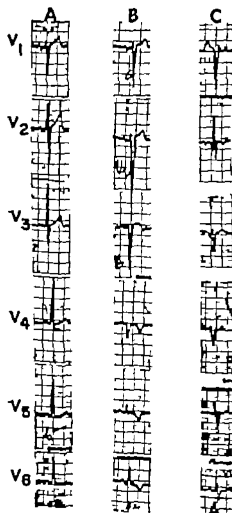


Fig. 2. Patient 10. Chest leads of June 26, 1961 (*A*) preceded the first infarct. The tracing of May 24, 1963 (*B*) was taken during the course of an acute anterolateral infarct. The tracing of Sept. 16, 1963 (C) was taken during the course of second infarct which proved to be anteroseptal at autopsy.

An autopsy study of the accuracy of the electrocardiogram in the diagnosis of recurrent myocardial infarction

Steven L. Merrill, M.D.
Morton Lee Pearce, M.D.
Los Angeles, Calif.

The value of the standard 12 lead electrocardiogram (ECG) as a means of diagnosing acute myocardial infarction is well established. In the majority of cases, it remains the most specific and accurate test leading to the diagnosis. Enzyme determinations serve primarily to support a diagnosis which is usually already established by the ECG. Old healed infarcts are usually identified by electrocardiographic abnormalities although a normal ECG does not exclude the possibility of previous myocardial infarction.[1,2] In one study, 128 patients were followed after myocardial infarction with ECG's; 31 per cent failed to show diagnostic evidence of the previous myocardial infarction one half to one year later.[3]

When myocardial infarction recurs in patients whose previous ECG's show evidence of an older infarction, the acute infarct pattern may be somewhat altered. Mussafia and Puddu,[4] reporting 60 cases, stated that most patients did not show typical ECG changes of the second infarct, the lack of early ST-T changes being particularly noticeable. In their study, two thirds of the second infarcts occurred in the same location as the first. Also of interest was the time interval between the first and second episodes. Five infarcts recurred within the first year, 23 between the first and second years, 20 between 2 and 5 years, 12 after 5 years, and one recurred after 13 years. In another study of 50 patients who died of myocardial infarction, 21 had autopsy evidence of a previous myocardial infarction which was recognized electrographically in only 9 of these patients. The authors stated that the most recent infarct made recognition of a previous one practically impossible. In their study, ECG's were available prior to the final episode in only 3 cases. Two additional patients had clinical histories of previous infarction.

There is a general impression that the ECG may not be as helpful in diagnosing recurrent myocardial infarctions as it is with initial infarcts. The present study was undertaken to evaluate the usefulness of the ECG in recurrent myocardial infarction.

Methods and materials

The charts of over 100 male patients whose autopsies showed evidence of acute

From the Veterans Administration Center, Los Angeles, Calif., and the Department of Medicine, University of California School of Medicine, Los Angeles, Calif.
Received for publication March 31, 1970.
Reprint requests to: Dr. Morton Lee Pearce, University of California, Los Angeles, Department of Medicine, School of Medicine, the Center for the Health Sciences, Los Angeles, Calif. 90024.

myocardial infarction were reviewed From this group 21 patients with clear-cut autopsy and clinical evidence of previous myocardial infarction(s) were selected The hospital records for the initial myocardial infarction and all subsequent hospitalizations, as well as the final hospital course resulting in death were carefully reviewed. The electrocardiograms were interpreted without knowledge of the clinical or pathological findings. Criteria for ECG diagnosis of infarction were the same as those used in a study previously reported by Dayton and associates.[4] The autopsy reports for each patient were reviewed and the location of healed as well as acute infarcts determined ECG's taken prior to the final episode showed evidence in each case of the previous myocardial infarction corresponding to areas of fibrosis reported at autopsy Interpretations of ECG's taken during the period

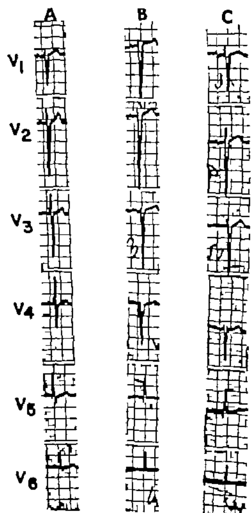


Fig 1 Patient 9 Chest leads of July 29 1958 (*A*) preceded the first infarct and are normal. The tracing of Feb. 13 1963 (*B*) was taken after his initial anteroseptal infarct. The final tracing (*C*) was taken 11 days before death (April 8, 1963) and shows little evidence of the acute anterolateral infarct found at autopsy

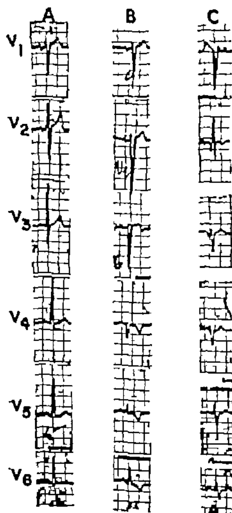


Fig 2. Patient 10. Chest leads of June 26, 1961 (*A*) preceded the first infarct. The tracing of May 24, 1963 (*B*) was taken during the course of an acute anterolateral infarct. The tracing of Sept. 16, 1963 (C) was taken during the course of second infarct which proved to be anteroseptal at autopsy

An autopsy study of the accuracy of the electrocardiogram in the diagnosis of recurrent myocardial infarction

Steven L Merrill M D
Morton Lee Pearce M D
Los Angeles Calif

The value of the standard 12 lead electrocardiogram (ECG) as a means of diagnosing acute myocardial infarction is well established In the majority of cases it remains the most specific and accurate test leading to the diagnosis. Enzyme determinations serve primarily to support a diagnosis which is usually already established by the ECG Old healed infarcts are usually identified by electrocardiographic abnormalities although a normal ECG does not exclude the possibility of previous myocardial infarction[1,2] In one study 128 patients were followed after myocardial infarction with ECG s 31 per cent failed to show diagnostic evidence of the previous myocardial infarction one half to one year later[3]

When myocardial infarction recurs in patients whose previous ECG s show evidence of an older infarction the acute infarct pattern may be somewhat altered Mussafia and Puddu[4] reporting 60 cases stated that most patients did not show typical ECG changes of the second infarct the lack of early ST T changes being particularly noticeable In their study two thirds of the second infarcts occurred in the same location as the first Also of interest was the time interval between the first and second episodes Five infarcts recurred within the first year 23 between the first and second years, 20 between 2 and 5 years 12 after 5 years, and one recurred after 13 years. In another study of 50 patients who died of myocardial infarction 21 had autopsy evidence of a previous myocardial infarction which was recognized electrographically in only 9 of these patients The authors stated that the most recent infarct made recognition of a previous one practically impossible In their study ECG s were available prior to the final episode in only 3 cases Two additional patients had clinical histories of previous infarction

There is a general impression that the ECG may not be as helpful in diagnosing recurrent myocardial infarctions as it is with initial infarcts. The present study was undertaken to evaluate the usefulness of the ECG in recurrent myocardial infarction

Methods and materials

The charts of over 100 male patients whose autopsies showed evidence of acu

From the Veterans Administration Center Los Angeles, Calif and the Department of Medicine University of California School of Medicine Los Angeles, Calif
Received for publication March 31 1970.
Reprint requests t Dr Morton Lee Pearce University of California, Los Angeles, Department of Medicine School of Medicine, the Center for the Health Sciences, Los Angeles, Calif. 90024.

infarction(s)

ECG findings		Final infarct correctly diagnosed by ECG	Findings for more than 2 infarcts (historical)	Location of recent infarct in relation to earlier one(s)
Prior to final infarct	After final infarct			
1962 old ASMI ant. ischemia and injury	4-19-63 old ASMI first degree A-V block, 4-23-63 increasing lat. ischemia second degree block with 2:1 response	No	No	Superimposed
12-8-62 old ASMI LVH with altered repolarization and/or ischemia	2-7-63 old ASMI IVCD ant.-lat. ischemia and post. ischemia, 2-8-63 increasing lateral subendocardial ischemia, ?acute LMI	Yes	? ASMI 1 yr. before final episode	Adjacent
2-2-63 acute AMI old DMI, RBBB	5-1-63 ant.-lat. ischemia, old AMI RBBB	No	Anterior MI 2/63	Superimposed
11-5-62 probable DMI ?age- abnormal ST T complexes, old AMI	3-19-63 acute DMI acute ASMI IVCD	Yes	N	Superimposed
2-8-63 old DMI ?ASMI, new lateral ischemia	2-12-63 LBBB, increasing lat. ischemia, ?acute lat. infarct	Yes	No	Superimposed
3-23-60 DMI, ?age lat. ischemia vs. dig. effect	5-15-63 old DMI increase ant.-lat. ischemia, ?subendocardial infarct	Yes	No	Distant
7-21-62 AMI DMI old new PMI	9-16-63 old post. and ant. MI anterior suggestive for aneurysm vs. recent MI	Yes	Historically had MI's on 4/58, 2/60, 7/62, 5/63 and 9/63	Superimposed
4-25-62 ASMI LVH with altered repolarization and/or ant.-lat. ischemia, probably LAH	1-9-63 LBBB	No	No	Adjacent-superimposed
2-21-62 old AMI	4-8-63 old AMI abnormal T waves, dig. effect	No	No	Superimposed
5-24-63 acute ALMI	9-20-63 old ALMI RBBB, ?lat. wall ischemia, acute ASMI	Yes	No	Adjacent
12-19-61 acute AMI ?DMI	9-3-63 old AMI, acute apical infarct	Yes	No	Distant
1-3-63 acute AMI, old lateral MI	1-23-63 atrial fibr. increase inf. and ant. lat. ischemia, evolving ASMI	Yes	No	Adjacent
12-28-60 old inferolateral MI	6-7-63 MI, ?age recent ALMI	Yes	No	Adjacent
12-6-60 old DMI	6-2-63 old DMI, acute AMI	Yes	No	Distant
3-20-63 ?old DMI borderline P waves, IVCD	4-3-63 old DMI acute ASMI	Yes	No	Distant
4-7-67 ASMI S-T segments isoelectric, T waves inverted V to V	4-30-67 S-T segments depressed V to V_6, T waves more deeply inverted; recurrent AMI	Yes	N	Superimposed-adjacent
12-19-66 old DMI, inverted T V_1-V	4-27-67 RBBB acute AMI old DMI, sinus tachycardia	Yes	No	Distant

Continued on next page

Table I Summary of 21 patients dying of acute myocardial infarction with known previous

Patient No	Date of death	Autopsy findings		Time between infarcts
		Location of acute infarct	*Location of old infarct(s)*	
1	4 28-63	Septal anterior and posterior involving moderator band (right coronary occlusion)	Anterior septal extending to apex	5 yr
2	2 9-63	Posterior lateral (right coronary thrombosis)	Anterior lateral, involving apex	10 yr
3	5-3-63	Midportion septal area	Posterior septal wall also	9 yr
4	3-20-63	Lateral with recent thrombosis, left circumflex and right coronary artery hemorrhagic areas posteriorly	Circumferential fibrosis, increase in ant. and post. areas	9 yr
5	2 12-63	Extensive posterolateral	Posterior ?Anterior	2 yr
6	5-23-63	Ant. incl papillary muscle 4 days–3 wk. subendocardial	Posterior from base to apex	3 yr
7	9-20-63	Anterior posterior	Anteroseptal, posterior ?diaphragmatic	1958, 1960, 1962, 1963 within 5 yr
8	1 17-63	Ant. lat. 1 1/2 wk with acute extension	Anteroseptal, ?fibrosis posteriorly	5 yr
9	4-19-63	Ant lat. recent thrombus left circumflex	Anteroseptal-lateral	5 yr
10	10-5-63	Anteroseptal	Anterolateral	5 mo.
11	9-9-63	Posterior-apical, septal	Anterior	2 yr
12	1 25-63	Anteroseptal lat., apical, 3 wk. 2 3 days duration	Lateral	6 yr
13	6-9-63	Anterolateral	Apical with aneurysm	5 yr
14	6-10-63	Anterolateral	Rt. coronary artery occlusion, patchy fibrosis	3 yr
15	4-4-63	Anteroseptal occlusion of left circumflex	Posteroseptal	1 yr
16	5-4-67	Anterolateral	Anteroseptal	1 mo.
17	4-28-67	Anteroseptal	Diaphragmatic	3 yr

ECG findings		Final infarct correctly diagnosed by ECG	Findings for more than 2 infarcts (historical)	Location of recent infarct in relation to earlier one( )
Prior to final infarct	After final infarct			
4-13-65 ASMI ?age lat. ischemia, LVH	2 13-67 acute ASMI, sinus tachycardia	Yes	No	Superimposed
5-21-66 old ASMI nonspecific ST T wave changes	3-30-67 acute ASMI	Yes	No	Superimposed
5-18-66 evolving DMI ?high posterior MI, RBBB	5-25-67 acute ALMI LVH, right ventricular dilatation, old DMI	Yes	Y	Adjacent
7-6-62 old ASMI ?aneurysm	4-6-67 acute DMI old ASMI	Yes	No	Distant

LMI left myocardial infarction; ALMI anterolateral myocardial infarction; MI myocardial infarction. LAH = left anterior hy

cent) the final infarct occurred in the same location as or closely adjacent to, the area of the previous infarct. All 4 cases where the final one was not diagnosed by the ECG were instances of acute myocardial infarction superimposed on pre existing areas of fibrosis. All new infarcts occurring in areas more distant from areas of old fibrosis were diagnosed by the ECG including an anterior-subendocardial in farct involving the papillary muscle (Patient 6)

Discussion

Neurath and Elek reported one patient who had a posterior (inferior) infarct with development of LBBB Five years later the diagnosis of an acute inferolateral infarct was made on the basis of deeper Q's in III and aV_F and S-T elevation in II III and aV_F Autopsy findings con firmed the ECG diagnosis. No other cases studied in a similar manner were found in the literature.

As in the case cited above in our series, all of the final infarctions were extensive enough to cause the patient's death. In other words, our selection was biased in favor of the more serious cases. Admittedly the degree of accuracy in diagnosing less extensive second infarcts may be appreciably less. Smaller initial infarcts are also diagnosed with considerably less accuracy by the ECG However the ECG does turn out to be a surprisingly good means of diagnosing recurrent even multiple episodes of myocardial infarction. In spite of rather extensive alteration of T waves S-T segments and pathological Q waves existing prior to a recurrent event, the ECG changes enough to make possible the diagnosis of a new acute episode in the majority of cases Further increases of pre-existing S-T-segment elevation or depression deeper inversion of already inverted T waves and further deepening and widening of pathological Q waves may all aid in making the diagnosis of a recurrent acute myocardial *infarction. In* the absence of these ECG findings, particularly in the light of good clinical findings, alterations in cardiac rhythm and development of intraventricular conduction disturbances should make one suspicious of an acute infarct. Frequent tracings are more important when dealing with second episodes of infarction as the changes may be subtler and may not occur as early in the course of the illness. However careful study of serial ECG's in a patient suspected of having a recurrent myocardial infarction will usually confirm the diagnosis, regardless of the location of acute necrosis in relation to pre-existing fibrosis, or of the ECG findings prior to the acute episode.

Table I —Cont d

Patient No	Date of death	Autopsy findings		Time betwe infarcts
		Location of acute infarct	Location of old infarct(s)	
18	2 13-67	Anteroseptal	Anteroseptal	2 yr
19	4 9-67	Anteroseptal	Anteroseptal	3 yr
20	5-28-67	Antero-apical	Posterior-inferior MI (right ventricle normal)	4 yr
21	4 7-67	Posterior inferior	Anteroseptal	11 yr

Abbreviations ASMI = nteroseptal myocardial inf rction; LVH = left entricular hypertrophy; DMI = diaphragmatic myocardial infarct pertrophy; Ant.-lat. = anterolateral.

of the final illness were then correlated with postmortem findings of acute necrosis

Results

The findings from the 21 patients are summarized in Table I Three of the 21 pa tients had more than one infarct prior to the final infarct. The final event was cor rectly diagnosed by the ECG in 17 of the 21 patients In 3 of the 4 patients in whom the diagnosis was not established by the ECG (Patients 3 8 and 9) the latest available tracings were taken from 6 to 11 days before the patient s death In all 4 cases the acute infarct was either super imposed on or closely adjacent to areas of fibrosis resulting from earlier myocardial infarction(s) In Patient 8 the one tracing taken during the final infarct showed left bundle branch block This was 8 days before the patient s death and serial tracings were not available In Patient 3 the acute infarct recurred in the septal area centered in an area of pre-existing fibrosis. Earlier tracings already showed RBBB Patient 1 developed second degree A V block with 2 1 response and T wave inversion in V_1 but showed no other changes of an acute infarct In Patient 9 the final available tracing was made 7 days before the patient s death Fig 1 compares the QRST complexes of the precordial leads taken on July 29 1958 Feb 13 1963 and April 8 1963 In this case Again there is little evidence of the acute anterolateral infarct which was found at autopsy However the sparsity of electrocardiographic tracings and the time lapse between the final ECG and the patient s death may again be factors

Patient 10 is an example where the cor rect diagnosis of recurrent infarction was made from the ECG although the last available tracing was made 16 days prior to the patient s death Fig 2 compares the QRST complexes of the precordial leads from tracings taken June 26 1961 May 24 1963 and Sept 16 1963 The acute infarct was adjacent to the pre-existing one Patient 18 had a final acute anteroseptal myocardial infarction super imposed on one which had occurred 2 yr previously Fig 3 illustrates the changes in the anterior precordial leads in tracings taken Aug 27 1958 Nov 8 1966 and Feb 13 1967 the day of the patient s death These 2 patients are characteristic of the 17 patients in the series in whom an ECG diagnosis of recurrent myocardial infarction was made

The median age of the patients at the time of death was 67 yr with a range from 46 to 84 The time from the first to the final myocardial infarction ranged from one month to 11 yr with a median of 4 45 yr In 15 of the 21 patients (71 per

Experimental and laboratory reports

Cardiovascular hemodynamics in the conscious dog

Robert A. O'Rourke, M.D.
Vernon S. Bishop, Ph.D.
Tucson, Ariz.

It is well known that anesthesia, thoracotomy, and artificial respiration all modify cardiac function.[illegible] Often the results of experiments on the anesthetized, open-chest animal cannot be substantiated in the awake animal.[illegible] It follows that concepts derived from experiments on the hearts of anesthetized, open-chest animals are not necessarily applicable to cardiovascular responses in intact unanesthetized man. For this reason, the conscious dog has been the subject of an increasing number of hemodynamic investigations.[illegible]

The investigator using this preparation has not had the benefit of a large body of control data with which to compare his own control or experimental results. The purpose of this paper is to present hemodynamic measurements obtained during control observations in 53 conscious dogs and to compare these results with those obtained by others.[illegible] All these data have been reported elsewhere as control data for various experimental interventions. An additional purpose of this communication is to compare control hemodynamics in conscious and anesthetized dogs.

Methods

Adult mongrel dogs were used in these studies. All cardiac output measurements were determined by the Fick principle, by the indicator dilution method, or with chronically implanted electromagnetic or ultrasonic flow probes. Electromagnetic transducers were calibrated in vitro before implantation, and during the actual measurements the late-diastolic level of aortic flow was used as the zero-flow reference point.[illegible] Calibration of the ultrasonic flowmeter was accomplished by substitution of fixed frequency sine-wave signals for the flow signals, zero-velocity corresponding to zero-frequency. The velocity signal obtained with the Doppler flowmeter was converted to flow by multiplying the integral of the velocity signal by the cross-sectioned area as calculated from post mortem internal aortic diameter measurements in each dog.[illegible]

Pressures were determined from chronically implanted catheters. These catheters were located in the right and left atrium, the internal thoracic artery, and the main pulmonary artery. At times arterial pressure was recorded using percutaneous puncture of the femoral artery. Pressures were recorded on a polygraph recorder using pressure transducers. The zero baseline was the midline of the sternum with the conscious dogs lying on their right sides.

The ventricular function curves were

From the Department of Medicine, University of Arizona, College of Medicine, Tucson, Ariz., and the Department of Pharmacology, University of Texas Medical School, San Antonio, Texas.
Received for publication March 2, 1970.
Reprint requests to: Dr. Robert A. O'Rourke, Division of Cardiology, Department of Internal Medicine, University Hospital of San Diego County, San Diego, Calif. 92103.

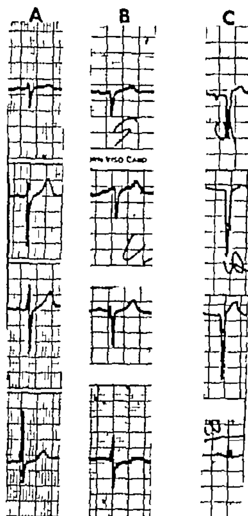


Fig 3 Patient 18 Chest leads V_1 to V_4. The tracing of Aug 27 1958 (*A*) precedes the first infarct. The tracing of Oct. 8 1966 (*B*) was taken after his first anteroseptal infarct. The tracing of Feb 13 1967 (*C*) was taken the day of death. At autopsy an acute anteroseptal infarct was found to be superimposed on an old one.

Summary

Electrocardiograms and autopsies of 21 patients dying of acute myocardial infarction with evidence of prior infarcts were studied The diagnosis of acute recurrent myocardial infarction was correctly made in 17 of 21 patients (81 per cent) The 4 new infarcts not diagnosed were all superimposed on areas of pre-existing fibrosis. In spite of pre-existing electrocardiographic abnormalities, careful study of repeated ECG s will generally result in the diagnosis of recurrent myocardial infarction

REFERENCES

1 Cox, C. J B : Return to normal of electrocardiogram after myocardial infarction, Lancet 1:194 1967
2 Kalbfleisch J M Shadakshorappa, K. S. Conrad L. L. and Sarkar N K. Disappearance of the Q-deflection following myocardial infarction, Amer. Heart J 76:193 1968.
3 Anderson, N and Skjaeggestad, O : The electrocardiogram in patients with previous myocardial infarction Acta Med Scand. 176:123 1964.
4 Mussafia A and Puddu N Electrocardiographic patterns in recurrent myocardial infarction, Geriatrics 23:132, 1968.
5 Gironi, G., and Giodice N ECG and anatomical pathological study of 21 cases of myocardial infarctions in subjects with a history of M I Folia Cardiol. (Milano) 26:254 1967
6 Dayton, S Pearce, M L., Hashimoto S. Dixon, W J and Tomiyasu, U : A controlled clinical trial of a diet high in unsaturated fat, Circulation 18(Suppl. II) July 1969
7 Neurath, O and Elek, S R. Recent and old posterior wall myocardial infarction Dis. Chest 39:323 1961

Table II Hemodynamic variables at the plateau of ventricular function curves

Author	Number of dogs (and weights)	Number of measurements	Heart rate (beats, min.)	Cardiac output (ml./min./Kg.)	Stroke volume (ml./beat/Kg.)	Systemic arterial pressure (mm. Hg)	Right atrial pressure (mm. Hg)	Left atrial pressure (mm. Hg)
1. Bishop et al.[28]	7 (no weights)	21	183 ± 8 S.E.	340 ± 20	1.9 ± 0.16		$\overline{10}$	$\overline{16}$
2. Bunn et al.[16]	8 (17 to 19 Kg.)	42	158 ± 8 S.E.	318 ± 13	1.0 ± 0.09		$\overline{14}$	$\overline{20}$
3. O'Rourke et al.[12]	8 (10 to 13 Kg.)	20	182 ± 7 S.E.	279 ± 4.9	2.1 ± 0.17	110 ± 3.7	$\overline{12}$	$\overline{16}$
4. Horwitz and Bishop[8]	6 (13 to 23 Kg.)	14	188 ± 12 S.E.	277 ± 23	1.8 ± 0.25	120 ± 8.0	—	$\overline{20}$

S.E. = the standard error of the mean.
Average rise was 11 mm. Hg ± 2.83 S.E.

The mean arterial pressure in 128 observations in 43 dogs ranged from 95 to 114 mm. Hg. The average right and left atrial pressures, ranged from 0.2 to 1.2 and 2.4 to 3.7 mm. Hg, respectively. Individual values for right atrial pressure ranged from 0 to 6 mm. Hg and for left atrial pressure from 0 to 8 mm. Hg. The mean pulmonary artery pressure was recorded in two of these studies and averaged 13.9 and 14.8 mm. Hg, respectively.

Table II shows hemodynamic measurements obtained at the plateau of ventricular function curves during 97 control observations in 27 conscious dogs. The average heart rate at the plateau of ventricular function ranged from 152 to 185 beats per minute. The cardiac output per kilogram of body weight increased at least two-fold from resting values and varied from 277 to 348 ml. per minute per kilogram. The average stroke volume per kilogram of body weight ranged from 1.8 to 2.1 ml. per beat per kilogram. These results demonstrate an increase in cardiac output at the plateau of the ventricular function curve which is due to an appreciable increase in both stroke volume and heart rate. The average increase in mean arterial pressure from the resting state to the plateau of the ventricular function curve varied from 11 to 20 mm. Hg. Peak left ventricular stroke work and left ventricular minute work were measured only during the first group of experiments.[28] A descending limb is always present when ventricular minute or stroke work is calculated during a rise in atrial filling pressure due to venous infusion. This is because arterial pressure and cardiac output reach constant values while atrial pressure continues to rise, thus producing a falling work output. For this reason, ventricular work curves, measured during the first group of experiments, were not calculated in subsequent experiments.

Discussion

The heart rates recorded in these conscious dogs are similar to values recorded by others (Table I). The wide range in heart rates is due to difference in training and in laboratory conditions. Heart rates recorded in well-trained, unanesthetized dogs[4, 15-17, 28] tend to be lower than heart rates obtained from the conscious, untrained dog.[13, 27, 37, 38] The average heart rate in the conscious dog is much less than in animals anesthetized with barbiturates which have an atropine-like effect.[7, 8] Chloralose, a frequently used hypnotic, also increases the heart rate,[31] while morphine reduces the heart rate in the intact dog.[30, 31]

There has been a wide range of cardiac outputs recorded in the unanesthetized dog. This variability is less marked when the cardiac output is expressed per square meter of body surface or per kilogram of body weight. The values obtained for cardiac output per kilogram are similar in all studies using the awake dog. During

Amer Heart J
January 1971

Table I Summary of resting hemodynamics in conscious dogs

Author	Number of dogs	Weight of dogs (Kg)	Number of measurements	Heart rate (beats/min.)	Cardiac output (ml./min or ml./min./Kg.)	Stroke volume (ml./beat or ml./beat/Kg.)	Systemic arterial pressure (mm. Hg)
1 Horwitz and Bishop[33]	10	13 to 23	22	90 ± 6.0 S.E.	118 ± 11.7(E)	1.30 ± 0.15*	93 ± 5.4
2 Stone and Bishop[34]	8	$\overline{16.7}$†	1	111 ± 8.5 S.E.	158 ± 21.6(E)	1.60 ± 0.30*	101 ± 3.0
3. Horwitz et al.[33]	11	1 to 16	33	103 ± 1 S.E.	170 ± 30.0(D)	1.30 ± 0.23*	—
4. Horwitz et al.[34]	10	12 to 16	20	108 ± 1.4 S.E.	194 ± 75.5(D)	1.82 ± 0.28	103 ± 11.3
5. O'Rourke et al.[13]	5	10 to 18	70	121 ± 7.5 S.E.	140 ± 12.7(F)	1.15 ± 0.13	98 ± 4.2
6. Stone et al.[35]	9	17 to 19	47	101 ± 4.0 S.E.	130 ± 8.0(F)	1.30 ± 0.06*	114 ± 4.0
7 Marshall[36]	5	1 to 20	90	85 ± 19.9 S.D.	2.32 ± 0.61(F)	—	—
8. Harrison and Leonard[26]	4	11 to 16	4	111 ± 27.8 S.D.	2.29 ± 0.19(F)	—	—
9 Stewart and Gilchrist[38]	5	11 to 15	6	17* ± 1.8 S.D.	—	—	—
10 Cohn and Stewart[37]	13	9 to 20	13	131 ± 29.8 S.D.	4.43 ± 1.52(F)	—	—
11 Gregg et al.[17]	16	18 to 27	16	83 ± 19.5 S.D.	2.86 ± 0.65(E)	32.9 ± 6.23	106 ± 11.6
12. Franck and Stahlgren[38]	9	10 to 12	27	88 ± 6.7 S.E.	157 ± 5.8(I)	—	96 ± 4.3
13. Steiner and Calvin[9]	7	16 to 22	7	93 ± 15 S.D.	3.71 ± 1.03 1 4 ± 25(E)	40 ± 5.0	109 ± 3.3
14 Barlow and Knott[1]	20	No weights	20	$\overline{83}$ ± 16 S.D.	$\overline{156}$ ± 30.0(I)	29 ± 8.4	$\overline{104}$ ± 6
15. Nash et al.[5]	10	10 to 1	10	$\overline{93.6}$	$\overline{3.02}$(I)	—	$\overline{137}$
16. Glick et al.[39]	10	11 to 1	10	$\overline{102}$ ± 0.0 S.D.	$\overline{103}$ ± 11(I)	1.93 ± 0.11	93 ± 3
17 Olmsted and Page[40]	34	18 to 1	59	$\overline{75}$	2.40(F)	—	85
18. Noble et al.[73]	16	22 to 33	11	170 ± 38.. S.D.	4.51 ± 1.43(E)	33 ± 10.8	105 ± 11.9

Abbreviation S.D. is one standard deviation S.E. is the standard error of the mean F is flow obtained by Fick principle; I is by indicator dilution technique E is with electromagnetic flowmeter and D is with Doppler ultrasonic flowmeter

* Value for cardiac output or stroke volume per kilogram of body weight.

†Line over number represent mean.

obtained by infusing Tyrode s solution into a large catheter in the superior vena cava in order to raise diastolic filling pressures.[12,21] The rate of infusion was controlled by a pressure bottle Increases in right and left atrial pressures systemic pressure and cardiac output were recorded during each infusion Generally infusion of 300 to 500 ml of Tyrode s solution over five minutes was necessary to reach the maximal cardiac output Further details of this method have been described previously [12,21] The actual function curves were obtained by plotting increase in cardiac output per kilogram of body weight on the ordinate and the increasing mean left and right atrial pressures on the abscissa

Results

One hundred and sixty-one control observations of resting hemodynamics in fifty three conscious dogs were made. These are listed in Table I as studies 1 through 6 For comparison Table I also lists various hemodynamic measurements in unanesthetized dogs as reported by other investigators [1,5,9,11,15,16,27-40]

The average heart rate in our six groups of untrained dogs ranged from 90 to 124 beats per minute This is somewhat higher than the heart rate obtained in trained conscious dogs under basal conditions (See Table I studies 11 13 15 18)

The average cardiac output ranged between 118 and 158 ml per minute per kilogram of body weight when measured by electromagnetic flowmeter and between 129 and 194 ml per minute per kilogram when measured by the Doppler ultrasonic flow probe The cardiac output per kilogram of body weight seemed to be rate dependent in the dogs with the lower resting heart rates but not in those with higher heart rates

The average stroke volume ranged from 1 15 to 1 82 ml per beat per kilogram of body weight and there was no definite correlation between increased heart rate and decreased strokes volume in these studies

Table II Hemodynamic variables at the plateau of ventricular function curves

Author	Number of dogs (and weights)	Number of measurements	Heart rate (beats/min.)	Cardiac output (ml./min./Kg.)	Stroke volume (ml./beat/Kg.)	Pulmonic arterial pressure (mm. Hg)	Right atrial pressure (mm. Hg)	Left atrial pressure (mm. Hg)
1. Bishop et al.[9]	7 (no weights)	21	185 ± 8 S.E.	340 ± 20	1.9 ± 0.16		13	16
2. Stone et al.[16]	9 (17 to 19 Kg.)	42	1?6 ± 8 S.E.	348 ± 13	1.9 ± 0.09		16	20
3. O'Rourke et al.[18]	5 (10 to 15 Kg.)	20	152 ± 7 S.E.	296 ± 4.9	2.1 ± 0.17	110 ± 4.7	12	18
4. Horwitz and Bishop[27]	6 (13 to 23 Kg.)	14	158 ± 12 S.E.	277 ± 28	1.8 ± 0.25	120 ± 8.0	—	[illegible]

S.E. is the standard error of the mean.
Average rise is 11 mm. Hg ± 2.45 S.E.

The mean arterial pressure in 128 observations in 43 dogs ranged from 95 to 114 mm. Hg. The average right and left atrial pressures, ranged from 0.3 to 1.2 and 2.4 to 3.7 mm. Hg, respectively. Individual values for right atrial pressure ranged from 0 to 6 mm. Hg and for left atrial pressure from 0 to 8 mm. Hg. The mean pulmonary artery pressure was recorded in two of these studies and averaged 13.9 and 14.8 mm. Hg, respectively.

Table II shows hemodynamic measurements obtained at the plateau of ventricular function curves during 97 control observations in 27 conscious dogs. The average heart rate at the plateau of ventricular function ranged from 152 to 185 beats per minute. The cardiac output per kilogram of body weight increased at least two-fold from resting values, and varied from 277 to 348 ml. per minute per kilogram. The average stroke volume per kilogram of body weight ranged from 1.8 to 2.1 ml. per beat per kilogram. These results demonstrate an increase in cardiac output at the plateau of the ventricular function curve which is due to an appreciable increase in both stroke volume and heart rate. The average increase in mean arterial pressure from the resting state to the plateau of the ventricular function curve varied from 11 to 20 mm. Hg. Peak left ventricular stroke work and left ventricular minute work were measured only during the first group of experiments.[9] A descending limb is always present when ventricular minute or stroke work is calculated during a rise in atrial filling pressure due to venous infusion. This is because arterial pressure and cardiac output reach constant values while atrial pressure continues to rise, thus producing a falling work output. For this reason ventricular work curves, measured during the first group of experiments, were not calculated in subsequent experiments.

Discussion

The heart rates recorded in these conscious dogs are similar to values recorded by others (Table I). The wide range in heart rates is due to difference in training and in laboratory conditions. Heart rates recorded in well-trained unanesthetized dogs[4, 11-13, 19] tend to be lower than heart rates obtained from the conscious untrained dog.[13, 17, 18, 24] The average heart rate in the conscious dog is much less than in animals anesthetized with barbiturates which have an atropine-like effect.[7, 8] Chloralose, a frequently used hypnotic, also increases the heart rate[7, 21] while morphine reduces the heart rate in the intact dog.[8, 9]

There has been a wide range of cardiac outputs recorded in the unanesthetized dog. This variability is less marked when the cardiac output is expressed per square meter of body surface or per kilogram of body weight. The values obtained for cardiac output per kilogram are similar in all studies using the awake dog. Durin

Table I Summary of resting hemodynamics in conscious dogs

Author	Number of dogs	Weight of dogs (Kg.)	Number of measurements	Heart rate (beats/min.)	Cardiac output (ml./min. or ml./min./Kg.)	Stroke volume (ml./beat or ml./beat/Kg.)	Systemic arterial pressure (mm. Hg)
1 Horwitz and Bishop[illegible]	10	13 to 23	22	90 ± 6.0 S.E.	118 ± 11.7(E)	1.30 ± 0.18	95 ± 5.4
2 Stone and Bishop[illegible]	8	$\overline{16.7}$†	21	111 ± 8.5 S.E.	156 ± 21.6(F)	1.90 ± 0.30*	101 ± 3.9
3 Horwitz et al.[illegible]	11	12 to 16	33	103 ± 1.7 S.E.	129 ± 30.0(D)	1.30 ± 0.23*	—
4. Horwitz et al.[illegible]	10	12 to 16	20	108 ± 1.4 S.E.	194 ± 23.5(D)	1.82 ± 0.26*	103 ± 11.8
5. O'Rourke et al.[13]	5	10 to 13	70	1 4 ± 7.5 S.E.	140 ± 12.7(F)	1.15 ± 0.13	98 ± 4.2
6. Stone et al.[illegible]	9	17 to 19	42	101 ± 4.0 S.E.	130 ± 6.0(F)	1.30 ± 0.06	114 ± 4.0
7 Marshall[illegible]	5	12 to 20	90	85 ± 18.0 S.D	2.32 ± 0.61(F)	—	—
8. Harrison and Leonard[illegible]	4	11 to 16	4	111 ± 27.3 S.D	2.29 ± 0.19(F)	—	—
9 Stewart and Gilchrist[illegible]	5	11 to 18	6	172 ± 21.8 S.D	—	—	—
10. Cohn and Stewart[illegible]	13	9 to 20	13	131 ± 29.8 S.D	4.43 ± 1.53(F)	—	—
11 Gregg et al.[illegible]	16	18 to 27	16	68 ± 18.5 S.D	2.86 ± 0.65(E)	32.9 ± 6.23	106 ± 11.6
12. Fronek and Stahlgren[illegible]	9	10 to 1	27	68 ± 6.7 S.E.	157 ± 5.8(I)	—	96 ± 4.3
13. Steiner and Calvin	7	16 to 22		93 ± 15 S.D	3.71 ± 1.03 174 ± 25(L)	40 ± 5.0	109 ± 3.3
14 Barlow and Knott[1]	20	No weights	20	83 ± 10 S.D	168 ± 25.0(I)	70 ± 8.4	$\overline{104}$ ± 6
15. Nash et al.	10	10 to 1	10	$\overline{93.6}$	$\overline{3.02}$(I)	—	$\overline{137}$
16. Glick et al.[illegible]	10	11 to 1	10	$\overline{107}$ ± 6.0 S.D	$\overline{192}$ ± 11(I)	1.93 ± 0.11	93 ± 2
17 Olmstead and Page[illegible]	34	18 to 1	59	$\overline{75}$	$\overline{2.40}$(E)	—	85
18. Noble et al.[illegible]	10	22 to 35	11	120 ± 29.2 S.D	4.51 ± 1.43(E)	38 ± 10.8	105 ± 11.9

Abbreviations S.D. is one standard deviation S.E. is the standard error of the mean F is flow obtained by Fick principle I is by indicator dilution technique E is with electromagnetic flowmeter and D is with Doppler ultrasonic flowmeter.
* Value for cardiac output or stroke volume per kilogram of body weight.
†Line over number represents mean.

obtained by infusing Tyrode's solution into a large catheter in the superior vena cava in order to raise diastolic filling pressures.[13,21] The rate of infusion was controlled by a pressure bottle. Increases in right and left atrial pressures, systemic pressure and cardiac output were recorded during each infusion. Generally, infusion of 300 to 500 ml. of Tyrode's solution over five minutes was necessary to reach the maximal cardiac output. Further details of this method have been described previously.[13,21] The actual function curves were obtained by plotting increase in cardiac output per kilogram of body weight on the ordinate and the increasing mean left and right atrial pressures on the abscissa.

Results

One hundred and sixty-one control observations of resting hemodynamics in fifty-three conscious dogs were made. These are listed in Table I as studies 1 through 6. For comparison, Table I also lists various hemodynamic measurements in unanesthetized dogs as reported by other investigators.[illegible]

The average heart rate in our six groups of untrained dogs ranged from 90 to 124 beats per minute. This is somewhat higher than the heart rate obtained in trained conscious dogs under basal conditions. (See Table I studies 11 13 15 18.)

The average cardiac output ranged between 118 and 158 ml. per minute per kilogram of body weight when measured by electromagnetic flowmeter and between 129 and 194 ml. per minute per kilogram when measured by the Doppler ultrasonic flow probe. The cardiac output per kilogram of body weight seemed to be rate dependent in the dogs with the lower resting heart rates but not in those with higher heart rates.

The average stroke volume ranged from 1.15 to 1.82 ml. per beat per kilogram of body weight and there was no definite correlation between increased heart rate and decreased strokes volume in these studies.

Table II. Hemodynamic variables at the plateau of ventricular function curves

Author	Number of dogs (and weights)	Number of measurements	Heart rate (beats/min.)	Cardiac output (ml./min./Kg.)	Stroke volume (ml./beat/Kg.)	Systemic arterial pressure (mm. Hg)	Right atrial pressure (mm. Hg)	Left atrial pressure (mm. Hg)
1. Bishop et al.[20]	7 (no weights)	21	185 ± 8 S.E.	340 ± 20	1.9 ± 0.16		$\overline{10}$	$\overline{16}$
2. Stone et al.	9 (17 to 19 Kg.)	42	166 ± 6 S.E.	318 ± 13	1.8 ± 0.09		$\overline{16}$	$\overline{20}$
3. O'Rourke et al.[19]	8 (10 to 15 Kg.)	20	152 ± 7 S.E.	296 ± 4.9	2.1 ± 0.17	110 ± 4.7	$\overline{12}$	$\overline{18}$
4. Horwitz and Bishop[20]	6 (18 to 23 Kg.)	11	158 ± 12 S.E.	277 ± 25	1.9 ± 0.23	120 ± 8.0	—	$\overline{20}$

S.E. is the standard error of the mean.
Average rise was 11 mm. Hg ± 2.83 S.E.

The mean arterial pressure in 128 observations in 43 dogs ranged from 95 to 114 mm. Hg. The average right and left atrial pressures, ranged from 0.2 to 1.2 and 2.4 to 3.7 mm. Hg., respectively. Individual values for right atrial pressure ranged from 0 to 6 mm. Hg and for left atrial pressure from 0 to 8 mm. Hg. The mean pulmonary artery pressure was recorded in two of these studies and averaged 13.9 and 14.8 mm. Hg respectively.

Table II shows hemodynamic measurements obtained at the plateau of ventricular function curves during 97 control observations in 27 conscious dogs. The average heart rate at the plateau of ventricular function ranged from 152 to 185 beats per minute. The cardiac output per kilogram of body weight increased at least two-fold from resting values, and varied from 277 to 348 ml. per minute per kilogram. The average stroke volume per kilogram of body weight ranged from 1.8 to 2.1 ml. per beat per kilogram. These results demonstrate an increase in cardiac output at the plateau of the ventricular function curve which is due to an appreciable increase in both stroke volume and heart rate. The average increase in mean arterial pressure from the resting state to the plateau of the ventricular function curve varied from 11 to 20 mm. Hg. Peak left ventricular stroke work and left ventricular minute work were measured only during the first group of experiments.[22] A descending limb is always present when ventricular minute or stroke work is calculated during a rise in atrial filling pressure due to venous infusion. This is because arterial pressure and cardiac output reach constant values while atrial pressure continues to rise, thus producing a falling work output. For this reason ventricular work curves, measured during the first group of experiments, were not calculated in subsequent experiments.

Discussion

The heart rates recorded in these conscious dogs are similar to values recorded by others (Table I). The wide range in heart rates is due to difference in training and in laboratory conditions. Heart rates recorded in well-trained unanesthetized dogs[3,13-17,20] tend to be lower than heart rates obtained from the conscious untrained dog.[17,21,20] The average heart rate in the conscious dog is much less than in animals anesthetized with barbiturates which have an atropine-like effect.[7] Chloralose, a frequently used hypnotic, also increases the heart rate[7,21] while morphine reduces the heart rate in the intact dog.[22,23]

There has been a wide range of cardiac outputs recorded in the unanesthetized dog. This variability is less marked when the cardiac output is expressed per square meter of body surface or per kilogram of body weight. The values obtained for cardiac output per kilogram are similar in all studies using the ...

experiments on 42 anesthetized dogs Wiggers[31] observed that the cardiac output was related to body weight In our experiments on the conscious dog there is also less variability in cardiac *output when it is* expressed per kilogram of body weight

The reported effects of anesthesia thoracotomy and artificial ventilation on the cardiac output in the dog have been inconsistent This is most likely due to variations in the depth of anesthesia at the time when hemodynamic measurements are made The stroke volume and cardiac output are diminished by the administration of pentobarbital sodium to dogs[1,6,7] Most authors conclude that cardiac output is mildly reduced under light barbiturate anesthesia and progressively decreases with increasing depth of anesthesia Shabetai Fowler and Hurlburt[7] studied the effect of morphine chloralose anesthesia on the cardiac output in dogs Cardiac output in these experiments averaged 112 ml per kilogram and varied by as much as 25 to 40 per cent when cardiac output was measured at 10 minute intervals. The authors concluded that a constant cardiac output cannot be obtained under morphine-chloralose anesthesia Recently Giles Quiroz and Burch[38] have demonstrated a progressive decrease in both *cardiac output and stroke volume during* urethane anesthesia in the intact dog

The effects of various anesthetics on blood pressure in the dog have been quite variable. Chloralose has been reported to increase the blood pressure in small doses[37] and to decrease the blood pressure in large doses.[38] Barbiturates injected rapidly markedly reduce the arterial blood pressure[39] and if barbiturate anesthesia is prolonged the blood pressure may further decrease. Both barbiturates and chloralose are frequently dissolved in the solvent propylene glycol prior to their intravenous administration A rapid intravenous infusion of propylene glycol itself may produce systemic *hypotension and cardiac arrhythmias.*[40] The arterial blood pressure also falls during the administration of morphine due to dilatation of the peripheral vessels.[42]

There is a reduction in cardiac output at the time of thoracotomy due to a decrease in venous return which results from the increase in intrathoracic pressure.[8] When positive pressure respiration is used in anesthetized dogs the gradient of pressure from peripheral to central veins is less and both cardiac output and stroke volume *are reduced*[4,41]

Measurements of phasic left coronary blood flow myocardial oxygen consumption and coronary arteriovenous oxygen difference have been recorded by Gregg *Khouri and Rayford*[17] *using an* electromagnetic flow probe implanted around the left main coronary artery or its branches In chronic unanesthetized dogs the left coronary blood flow ranged from 37 to 58 ml per 100 grams of left ventricle per minute and myocardial oxygen consumption from 4 4 to 8 6 ml per 100 grams of left ventricle per minute The coronary arteriovenous oxygen difference ranged from 11 to 15 ml per 100 ml

The first derivative of the left ventricular pressure curve has been recorded by Noble and co-workers[18] in the unanesthetized dog using a micromanometer tip catheter implanted in the left ventricle The average value obtained for dp/dt was 1 *912* mm Hg per second with a range of 960 to 2 740

Measurements of hemodynamic parameters in conscious dogs during varying degrees of treadmill exercise have been made *by several investigators.*[43-47] *In* general these studies show a two- to three fold increase in cardiac output with a much greater increase in heart rate than in stroke volume. There is a variable increase in both mean arterial pressure and mean atrial pressures.

Ventricular output curves which quantitate cardiac performance during rapid intravenous infusion by measuring ventricular output as a function of the increased mean atrial pressure have been used by us to estimate cardiac reserve in conscious animals. These ventricular output curves are based upon the Frank Starling principle and are reproducible in control animals. The plateau values for cardiac output are depressed in dogs with radiation induced myocardial necrosis[17] and elevated in animals infused intravenously with the beta adrenergic agent isoproterenol[48] thereby reflecting changes in the inotropic state of the myocardium *Recent measure*ments of the internal diameter of the left

ventricle by a sonomicrometer during the plateau of the left ventricular curves in conscious dogs suggest that the elevation in stroke volume obtained by the volume load is due primarily to an increase in the diastolic size of the ventricle.[4]

Hemodynamic data obtained from the conscious dog may differ greatly from values obtained in the open-chest anesthetized animal. There is usually a significant difference between the unanesthetized and anesthetized animal in cardiac output, heart rate, and mean arterial pressure. Data obtained in the anesthetized open-chest animal often cannot be substantiated in the awake animal. A given experimental intervention may produce different changes in cardiovascular hemodynamics in the same experimental model under different types of anesthesia.[11] These facts must be kept in mind when attempting to interpret cardiovascular data obtained during experimental intervention in the anesthetized animal and when attempting to relate this data to cardiovascular responses in intact, unanesthetized man.

Summary

Hemodynamic measurements obtained during 161 control observations in 53 conscious dogs are reported and compared to the results obtained by other investigators. Average cardiac output varied from 118 to 194 ml. per minute per kilogram of body weight, average stroke volume from 1.15 to 1.82 ml. per beat per kilogram of body weight, and heart rate from 90 to 124 beats per minute in cooperative but untrained dogs. Mean systemic arterial pressure varied from 95 to 114 mm. Hg and mean pulmonary artery pressure from 13.9 to 14.8 mm. Hg.

Hemodynamic measurements made at the plateau of ventricular function curves obtained by rapid volume infusion, are also reported. Ninety-seven function curves were obtained in 27 conscious dogs. The cardiac output increased two- to three-fold from resting values with appreciable increases in both stroke volume and heart rate.

REFERENCES

1. Barlow, G., and Knott, D. H.: Hemodynamic alterations after 30 minutes of pentobarbital sodium anesthesia in dogs, Amer. J. Physiol. 207:764, 1966.
2. Caldini, P., Ho, C., and Zingg, W.: Effect of thoracotomy on cardiac output and pulmonary hemodynamics in dogs, J. Thorac. Cardiovasc. Surg. 44:104, 1962.
3. Fermoso, J. P., Richardson, T. P., and Guyton, A. C.: Mechanisms of decrease in cardiac output caused by opening the chest, Amer. J. Physiol. 207:112, 1964.
4. Morgan, B. C., Martin, W. E., Hornbein, T. F., Crawford, E. W., and Guntheroth, W. G.: Hemodynamic effects of intermittent positive pressure respiration, Anesthesiology 27:584, 1966.
5. Nash, C. B., Davis, F., and Woodbury, R. D.: Cardiovascular effects of anesthetic doses of pentobarbital sodium, Amer. J. Physiol. 185:107, 1956.
6. Rushmer, R. F., Smith, O., and Franklin, D.: Mechanisms of cardiac control in exercise, Circ. Res. 7:602, 1959.
7. Shabetai, R., Fowler, N. O., and Hurlburt, O.: Hemodynamic studies of dogs under pentobarbital and morphine chloralose anesthesia, J. Surg. Res. 3:263, 1963.
8. Smith, L. L., Foster, R. L., and Muller, W.: Intrinsic cardiac output variability in the anesthetized normal splenectomized dog, Amer. J. Physiol. 202:1155, 1962.
9. Steiner, S. H., and Calvin, J. R.: The effect of anesthesia with pentobarbital on hemodynamics and arterial blood gases in splenectomized dogs, J. Thorac. Cardiovasc. Surg. 81:592, 1967.
10. Burch, G. E.: Of the normal dog, Amer. Heart J. 68:805, 1959.
11. Giles, T. D., and Burch, G. E.: Anesthesia, dogs and cardiovascular data, Amer. Heart J. 79:141, 1970.
12. Morrison, J. L., Walker, H. A., and Richardson, A. P.: Effect of pentobarbital on response of cardiovascular systems of dogs to epinephrine, acetylcholine, and tilting, Arch. Int. Pharmacodyn. 82:33, 1950.
13. O'Rourke, R. A., Bishop, V. S., Stone, H. L., and Rapaport, E.: Lack of effect of procaine amide on ventricular function of conscious dogs, Amer. J. Cardiol. 23:238, 1969.
14. Price, H. L.: General anesthesia and circulatory homeostasis, Physiol. Rev. 40:187, 1960.
15. Fronek, K., and Stahlgren, L. L.: Systemic and regional hemodynamic changes during food intake and digestion in non-anesthetized dogs, Circ. Res. 23:687, 1968.
16. Glick, G., Plauth, W. H., and Braunwald, E.: Circulatory responses to hypoxia in unanesthetized dogs with and without cardiac denervation, Amer. J. Physiol. 207:753, 1964.
17. Gregg, E. D., Khouri, E. M., and Rayford, C. R.: Systemic and coronary energetics in the resting, unanesthetized dog, Circ. Res. 16:102, 1965.
18. Hinomiya, I., and Wilson, M. F.: Analysis of ventricular dimension in the unanesthetized dog, Circ. Res. 16:249, 1965.
19. Noble, M. E., Gabe, I. T., Trenchard, D., and

Cux, A. Blood pressure and flow in the ascend ing aorta of conscious dogs, Cardiovasc. Res. 1:9 1967
20. Olmstead F and Page I H: Hemodynamic changes in trained dogs during experimental renal hypertension Circ. Res. 16:134 1965.
21 Bishop, V S. Stone, H L. and Guyton, A. C. Cardiac function curves in conscious dogs, Amer J Physiol. 207:677 1965
22 Horwitz, L. D and Bishop V S Effects of ouabain on left ventricular performance in conscious dogs, Cardiovasc. Res. 4:31 1970
23 Horwitz L. D Bishop, V S., and Stone H L. Effect of hypercapnia on the cardiovascular system of conscious dogs, J Appl Physiol. 25:346 1968.
24 Horwitz L. D Bishop V S Stone H L. and Stegall H F Cardiovascular effects of low oxygen atmosphere in conscious dogs and anesthetized dogs, J Appl. Physiol. 27:370 1969
25 Stone H L. and Bishop V S Ventricular out put in conscious dogs following acute vagal blockade, J Appl Physiol. 24:782 1968.
26. Stone, H L., Bishop, V S and Dong, E. Ventricular function in cardiac-denervated and cardiac-sympathectomized conscious dogs, Circ. Res. 20:587 1967
27 Cohn A. and Stewart H J The relation between cardiac size and cardiac output per minute following the administration of digital s in normal dogs, J Clin. Invest. 6:53 1928.
28 Marshall E. K The cardiac output of the normal unanesthetized dog, Amer J Physiol 77:459 1926.
29 Stewart, H J and Gilchrist R. A. Studies on the effect of cardiac irregularity on the circ la tion. II The estimation of cardiac output i dogs subject to artificial auricular fibrillation J Clin. Invest. 5:535 1927
30 Harrison T R. and Leonard B W The effect of digitalis on the cardiac output of dogs and t bearing on the action of the drug in heart disease, J Clin. Invest. 3:1 1926.
31 von Luda y G Dier Wirkung der Chloralose auf das Elecktrokardiogramm. Z Pharmakologie der Chloralose Arch Exper Path Pharmakil. 167:717 1932
32 McCrea, F D and Meek, W J Action of morphine in slowing pulse J Pharmacol Exp. Ther 47:411 1933
33 Schmidt, C. \ and Livingstone, A. E. Action of morphine i the mammalian circulation J Pharmacol. Exp Ther 47:411 1933
34. Wiggers, H C. Cardiac output and peripheral resistance, Amer J Physiol. 140:519 1944
35 Giles, T D Quiroz, A. C. and Burch, G E. Hemodynamic alteration produced by prolonged urethane anesthesia in the intact dog, Amer. Heart J 78:281 1969
36. Holt, J P Effect of positive and negative intrathoracic pressure on cardiac output in venous pressure in dogs, Amer J Physiol. 112:594 1954
37 Vincent S and Thompson, J H Pharmacodynamical action of chloralose, J Physiol. (London) 56:149 1928
38. Raymond Hamet M Action du chloralose sur le sympathique et le parasympathique Compt Rend 186:101 1928.
39 Hamilton, W F Pund, E. R Slaughter R. S., Simptons, W A., Coslon, G. M Coleman, H W and Bateman W H Blood pressure values in street dogs, Amer J Physiol 128:233 1940.
40 Louis, F., Kutt, H McDowell F The cardiocirculatory changes caused by intravenous dilantin and its solvent, Amer. Heart J 4:523 1967
41 Barger A. C. Richards, V Metcalfe, J and Gunther B Regulation of the circulation during exercise. Cardiac output (d rect Fick) and metabolic adjustments in the normal dog, Amer J Physiol. 184:613 1956.
42 Cerretelli, P P per J., Mangili F Cutica F and Ricci B Circulation in exercising dogs, J Appl Physiol. 19:29 1964
43 Croni R. F Hemodynamic and metabolic effects of beta adrenergic blockade n exercising dogs, J Appl Physiol 22:211 1967
44 Donald, D E., and Ferguson, D Response to heart rate, oxygen consumption and arterial blood pressure to graded exercise in dogs, Proc. Soc. Exp. Biol Med 121:626 1966.
45 Khouri, E. M Gregg E. D and Rayford C R. Effects of exercise on cardiac output, left coronary flow and myocardial metabolism n the nanesthetized dog Circ. Res. 1 :427 1965
46. Schenk, W G. Delin A. N Kjartansson B and Pollock L. Cardiovascular studies in the exercising animal Cardiac output, arterial pressure cardiac work and blood gas studies in the normal dog and the dog with heart block under maximal exercise. Methods and preliminary results, J Thorac. Cardiovasc. Surg 51:854 1966.
47 Stone H L. Bishop, V S. and Guyton, A. C. Ventricular f nction following radiation damage of the right ventricle, Amer J Physiol 221 1209 1966.
48. Bishop, V S. Unpublished data.
49 Bishop, V S Horwitz, L. D Stone, H. L. Stegall H S. and Engelken, E. J Left ventricular internal diameter and cardiac f nction in conscious dogs, J Appl Physiol 27:619 1969

Ventricular function following acute alcohol administration: A strain-gauge analysis of depressed ventricular dynamics

Walter H. Newman, Ph.D.
Joseph F. Valicenti, Jr., M.S.
Charleston, S. C.

A particularly significant problem concerning acute alcoholism is the increased susceptibility of the acutely intoxicated to trauma and shock. Cournand[1] observed that acutely intoxicated patients frequently developed shock out of proportion to their blood loss. Similar findings in acutely intoxicated dogs demonstrate an impairment of the cardiovascular response to abrupt hemorrhage.[2,3] Further, Webb and associates[4] reported that rapid transfusion commonly produced cardiac arrest in intoxicated dogs. Since myocardial depression is a recognized feature of acute alcoholism[5] and could be involved in this altered response to trauma, this study examines the depressed ventricular dynamics and compensatory mechanisms following sublethal infusions of ethyl alcohol.

An examination of ventricular dynamics must consider at least the two major factors determining ventricular performance. The first is the load the ventricle works against and the second is contractility or inotropic state of the ventricle. Currently load is subdivided into preload and afterload. Preload, the force or stress in the ventricular muscle fiber which determines its diastolic length, is a function of ventricular diastolic pressure and size.[6] Afterload represents the force on the ventricle once it begins to eject and is a function of ventricular size and aortic diastolic pressure.[6] The second factor, contractility or inotropic state, has been related to the maximum rate of ventricular pressure rise (dp/dt), the maximum velocity of shortening of the muscle fiber or the contractile elements (Vmax) and to the peak of the curve recorded with the Walton Brodie strain-gauge arch (CF). This present investigation describes strain-gauge methodology for continuously monitoring changes in contractility and ventricular loading conditions. Additionally, for comparison with alcohol, equivalent depression of CF was produced by pentobarbital. Further

From the Department of Pharmacology, Medical University of South Carolina, Charleston, S. C.
This study was supported by Grants HE-00049 and HE-12574 from the National Heart and Lung Institute and funds from the South Carolina Heart Association.
Received for publication March 6, 1970.
Reprint requests to: Dr. Newman, Department of Pharmacology, Medical College of South Carolina, 80 Barre St., Charleston, S. C. 29401.
*United States Public Health Service Trainee HE-05288.

Ventricular function following acute alcohol administration: A strain-gauge analysis of depressed ventricular dynamics

Walter H. Newman, Ph.D.
Joseph F. Valicenti, Jr., M.S.
Charleston, S. C.

A particularly significant problem concerning acute alcoholism is the increased susceptibility of the acutely intoxicated to trauma and shock. Cournand[1] observed that acutely intoxicated patients frequently developed shock out of proportion to their blood loss. Similar findings in acutely intoxicated dogs demonstrate an impairment of the cardiovascular response to abrupt hemorrhage.[2] Further, Webb and associates[3] reported that rapid transfusion commonly produced cardiac arrest in intoxicated dogs. Since myocardial depression is a recognized feature of acute alcoholism[4] and could be involved in this altered response to trauma, this study examines the depressed ventricular dynamics and compensatory mechanisms following sublethal infusions of ethyl alcohol.

An examination of ventricular dynamics must consider at least the two major factors determining ventricular performance. The first is the load the ventricle works against and the second is contractility or inotropic state of the ventricle. Currently load is subdivided into preload and afterload. Preload, the force or stress in the ventricular muscle fiber which determines its diastolic length, is a function of ventricular diastolic pressure and size.[5] Afterload represents the force on the ventricle once it begins to eject and is a function of ventricular size and aortic diastolic pressure.[6] The second factor, contractility or inotropic state, has been related to the maximum rate of ventricular pressure rise (dp/dt), the maximum velocity of shortening of the muscle fiber or the contractile elements (Vmax) and to the peak of the curve recorded with the Walton-Brodie strain-gauge arch (CF). This present investigation describes strain-gauge methodology for continuously monitoring changes in contractility and ventricular loading conditions. Additionally, for comparison with alcohol, equivalent depression of CF was produced by pentobarbital. Further

From the Department of Pharmacology, Medical University of South Carolina, Charleston, S. C.
This study was supported by Grants HE-[illegible] and HE-[illegible] from the National Heart and Lung Institute and funds from the South Carolina Heart Association.
Received for publication March 4, 1970.
Reprint requests to: Dr. Newman, Department of Pharmacology, Medical College of South Carolina, 80 Barre St., Charleston, S. C. 29401.
*United States Public Health Service Trainee [illegible].

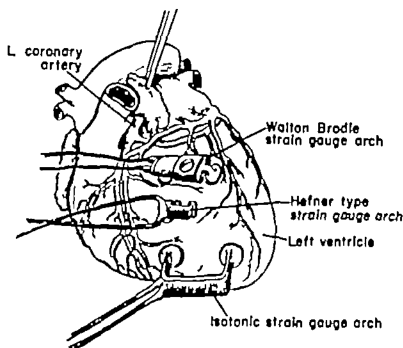


Fig 1 Left ventrolateral view of the heart with three types of strain gauge arches sutured to the myocardium. The Walton-Brodie Hefner type and isotonic strain-gauge arches record respectively contractile force, mural force and muscle-segment length A deep transverse incision, made between the feet of the Hefner arch, transfers force within the wall of the ventricle to the beam of the arch.

ouabain infusion essentially reversed the severe cardiac depression produced by alcohol or pentobarbital

Methods

Reported experiments were performed on 12 mongrel dogs of both sexes weighing from 12 5 to 23 kilograms under intravenous sodium pentobarbital anesthesia (30 mg per kilogram) The animals were ventilated with room air using a Harvard 607 respirator with a volume of 20 ml per kilogram and respiratory rate of 12 to 16 per minute The right femoral artery and vein were cannulated and aortic pressure (AP) was recorded by a Statham P23AA pressure transducer The chest was entered through the left fifth intercostal space The heart was exposed and the pericardium opened and sutured to the chest wall Three strain-gauge arches were then sutured to the myocardium as shown in Fig 1 They were (1) a Walton Brodie strain-gauge arch designed to measure myocardial contractile force (CF) (2) an isotonic strain gauge arch designed to respond to changes in muscle segment length (MSL) and (3) a Hefner type strain-gauge arch designed to respond to the force developed within the wall of the left ventricle mural force (MF) [7] Although both the Walton Brodie and Hefner type strain-gauge arches were isometric they responded to two distinctly different forces generated in the ventricular wall Recordings with the Walton Brodie strain gauge arch attached at 40 per cent stretch represent forces which are determined primarily by the active contractile property of the myocardium and are essentially unaltered by changes in preload or afterload Such forces act in a direction tending to pull the feet of this isometric gauge together The Hefner type strain-gauge arch in contrast responds to forces tending to separate the points of attachment Such forces in the intact ventricle are described by the Laplace principle ($F \alpha PA$) * Therefore in contrast to forces recorded with the Walton Brodie arch forces recorded by the Hefner arch are uniquely determined by loading conditions i e. alterations in ventricular pressure or size. To record these

*F = Force; P = pressure; A = cross sectional area of the ventricular cavity

forces the gauge was attached to the myocardium with deep sutures and then a transverse incision was made between the feet of the arch to a depth of approximately two thirds the thickness of the ventricle Thus the force originally supported by the muscle was transferred to the arch.

Of the 12 animals employed for this study half were subjected to slow (25 minutes) randomly alternate intravenous infusions of alcohol (2 Gm. per kilogram) 40 per cent (volume/volume) in saline and sodium pentobarbital (30 mg per kilogram) in equal volume and rate. The remaining animals were infused with two successive infusions of alcohol. Venous blood samples were obtained 5 minutes following initial alcohol infusion and blood alcohol content was determined by the method of Aull and McCord [8] Following initial depression with either alcohol or pentobarbital all parameters were allowed to stabilize before the second infusion was made. Following this, a steady state was again obtained at which time ouabain (0 025 mg per kilogram) was administered by slow (15 minute) intravenous infusion. This initial ouabain infusion was supplemented with doses of 0 005 mg per kilogram until digitalization was evidenced by a typical increase in CF Alterations in the four parameters—CF MF MSL, and AP—were recorded on a Grass 5 polygraph.

In three experiments, which were subjected to more critical analysis, rectilinear recordings were made on a Sanborn 150 Viscorder In these three experiments, left ventricular pressure (LVP) was monitored by passing a stiff nylon catheter connected to a Statham P23AA pressure transducer into the left ventricular chamber at the apical dimple.

Probability values reported in the text were obtained from the Student "t" test for the difference between means. Correlation coefficients and probability analysis are according to Snedecor [9]

Results

The response to a single slow intravenous infusion of alcohol is illustrated in Fig 2 CF was depressed, MF elevated and ventricular circumference, as indicated by the change in MSL was increased. AP was

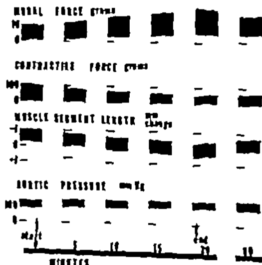


Fig. 2. Typical cardiovascular depression produced by slow intravenous infusion of alcohol (2 Gm. per kilogram) diluted to 40 per cent in saline. Paper speed = 0.025 mm. per second.

essentially unchanged. Following a recovery period of one hour the parameters returned toward control but failed to reach original values. Five minutes following the initial alcohol infusion venous samples had a mean blood alcohol content of 273 ± 19.8 with a range of 254 to 309 mg per cent.

Fig 3 is representative of a typical pentobarbital infusion. The initial responses appeared to be similar to those produced by alcohol i.e., depression of CF increase in ventricular circumference and an increase in MF with relatively little change in AP However near the end of the pentobarbital infusion, AP decreased This fall in AP was accompanied by a decreased pressure distending the ventricle resulting in shortening of the muscle segment. The net result of these two factors was a reduction of the previously increasing MF Unlike alcohol in which all parameters were at maximum change at end infusion time, only AP and CF were similarly affected by pentobarbital. As with alcohol once the infusion had been terminated all parameters shifted toward control, but never completely reached control values even after periods as long as one hour

Following the end of the second depressant drug infusion, a 60 minute recovery

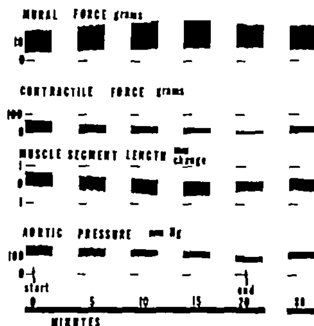


Fig 3 Representative response to slow intravenous infusion of sodium pentobarbital (30 mg per kilogram) Paper speed = 0.025 mm. per second

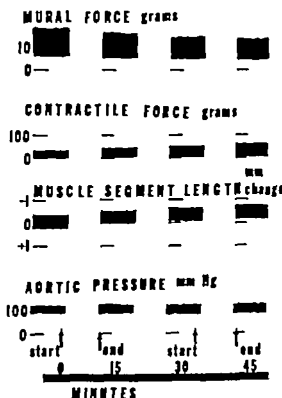


Fig 4 Typical reversal of depression produced by 15 minute ouabain infusions (0 025 mg per kilogram) and supplement (0.005 mg per kilogram) Paper speed = 0.025 mm. per second

period was allowed before ouabain was administered Fig 4 represents a typical response to ouabain infusion Contractile force was increased MSL was shortened and MF was reduced In all 12 experiments infusion of ouabain was followed by a return of all parameters toward the control values that existed prior to the acute cardiac depression

Fig 5 summarizes the changes in MF MSL diastolic AP and CF in 12 animals following the second drug depression produced by the administration of alcohol and/or pentobarbital All measurements were made at the end of isovolumic systole The values designated after depression describe the steady state following alcohol or pentobarbital infusion and conditions when ouabain infusion was begun After ouabain corresponds to peak effects associated with the administration of ouabain The results of paired data analysis indicate that CF MF and MSL are significantly altered from control after alcohol or pentobarbital ($p < 0.05$) Also these same parameters similarly analyzed show significant changes toward control after ouabain administration ($p < 0.05$)

In order to relate MF changes to load changes produced in the ventricle by alcohol pentobarbital and ouabain administration a correlation was obtained between the variables mural force and the product of intraventricular pressure multiplied by an index of internal radius squared (PR_i^2) Pressure and mural force values were recorded directly Estimates of internal radius were obtained from MSL recordings by the method previously described [10] High speed rectilinear recordings (100 mm per second) allowed all measurements to be made at the point of peak MF which closely coincides with the end of isovolumic systole Data obtained from three separate experiments are illustrated in Fig 6 The graphs show a high correlation between MF and PR_i^2 for data taken randomly throughout infusion and recovery from the depressant drugs and reversal of the depression following by ouabain The probability values indicate a highly significant relation between the measured MF and the load on the ventricle

Discussion

Alcohol induced cardiac dilation has been frequently documented in the literature.[4, 11] However little attention has been directed

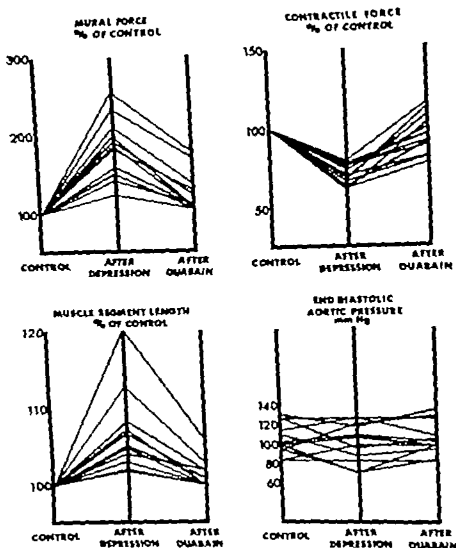


Fig. 3 Changes in aortic pressure, left ventricular mural force, contractile force, and muscle-segment length produced by alcohol or pentobarbital followed by ouabain. Control represents values prior to any drug administration. *After depression* represents measurements obtained after the second cardiovascular depression produced by alcohol or pentobarbital and just prior to ouabain infusion. *After ouabain* represents values approximately 45 minutes after the beginning of ouabain infusion.

toward the relationship between this change in cardiac size and the impaired myocardial function observed in acute alcoholism. The significance of cardiac size with regard to myocardial function has been discussed by Burch and co-workers.[13] In accord with the Laplace principle, the load placed on the heart increases as cardiac size increases in order to expel a given stroke volume against a constant diastolic aortic pressure. Such an increase in ventricular load results in increased myocardial energy demands and decreased myocardial efficiency.[13,14] Heart muscle compensates for an increased load with increased contractility by two primary mechanisms. One is an increase in CF by a positive influence on the inotropic environment through neurogenic or chemical mechanisms and which is independent of fiber length changes. The second is the Frank Starling phenomenon in which an increase in fiber length (diastolic heart size or preload) is accompanied by an increase in CF through a limited range of increased fiber length.

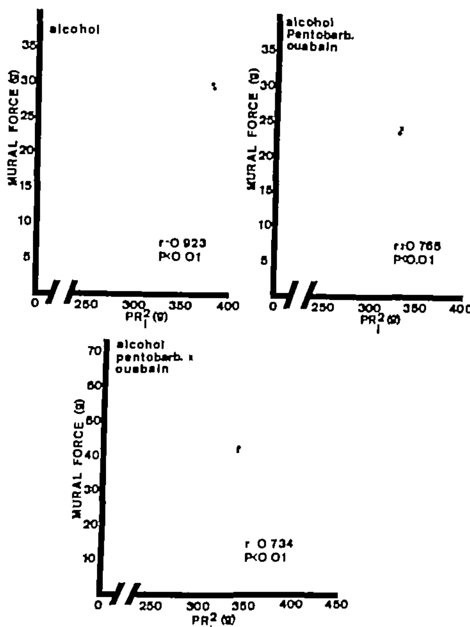


Fig 6 Data obtained from three separate experiments yield a highly significant correlation of mural force (MF) with distending force PR^2 Determinations were made at varying intervals during and following drug infusion. All measurements were taken at peak MI (the end of isovolumic contraction) r = Correlation coefficient p = probability PR_i^2 = product of left ventricular pressure and the square of the internal radial index.

In this present study the load on the heart and changes in CF were assessed by strain gauge techniques. In these experiments MF measured with the Hefner gauge was used as a directly recorded index of the load since measurements with this gauge have been shown to correlate with PR^2 the total force in grams at the equator of the ventricle [7,10] Measurements of CF with the Walton Brodie arch reflect changes in contractile processes as influenced by neurogenic and chemical means and are relatively uninfluenced by changes in heart size or arterial blood pressure [11] Changes in CF occurring in the myocardial segment subtended by this arch have been shown to represent homogeneous CF changes in the surrounding myocardium [11] These measurements of CF since length is fixed cannot reflect changes in the contractile process produced by length tension relationship Changes in MSL an index of ventricular radius were obtained with an isotonic strain gauge and were employed to define length-dependent changes in contractility This isotonic arch has been

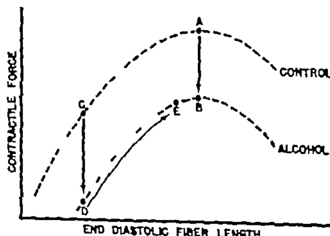


Fig. 7 Ventricular compensation to a increased load produced by alcohol infusion. See text for explanation.

shown to respond to ventricular size and shape change occurring during the cardiac cycle and its dynamic characteristics have been described elsewhere.

Fig 7 describes the altered ventricular dynamics produced by alcohol infusion and illustrates the principles of assessing ventricular function with strain gauges. The CF length curves shown in the figure were not directly measured in these experiments but represent typical curves obtained with a Walton-Brodie arch with adjustable feet.[15,17] Point A describes CF recorded with the Walton-Brodie arch from a muscle segment which has been stretched 40 per cent and held at this length. This degree of stretch has been shown to be at or very near the peak of the CF length relationship.[17] Point B represents the depression of CF measured in these present studies, following the alcohol infusion. Symmetrical alterations in the CF-length relation produced by positive and negative inotropic interventions resulting in a family of curves have been demonstrated by Reeves and Hefner[18] It is *therefore* assumed that Point B also describes a symmetrical depression of the CF length relationship. Point C, on the control curve, represents the contractile state of the myocardium which was not stretched by the Walton-Brodie arch. The exact position of Point C on the CF length curve in the open-chest dog is unknown however the ventricle of the open-chest dog responds to increased aortic pressure with increased stroke work. This type of response indicates that length-dependent increases in CF are operative in the open-chest dog and that Point C may be assumed to be on the ascending limb of the curve Point D indicates the shift produced by alcohol and represents the contractile state of the myocardium not stretched by the Walton-Brodie arch Compensation for the increased load i.e., increased MF produced by alcohol was accomplished by increased CF through length-dependent mechanism as evidenced by the increase in MSL reported in these experiments This length dependent compensatory increase in contractility is represented by Point E. The exact position of Point E on the ascending limb cannot be described from these experiments but measurements reported here support the view that the functioning level of the ventricle is nearer the limit of Frank Starling compensatory mechanisms following alcohol. An essentially similar alteration followed pentobarbital infusions.

These alcohol effects were reversed by ouabain. CF increased and cardiac size decreased with a concomitant reduction of MF It appears that the influence of ouabain on CF produces a greater degree of emptying resulting in a smaller end diastolic volume This therefore reduces ventricular load and increases the mechanical advantage which in turn would result in a more complete emptying of the ven

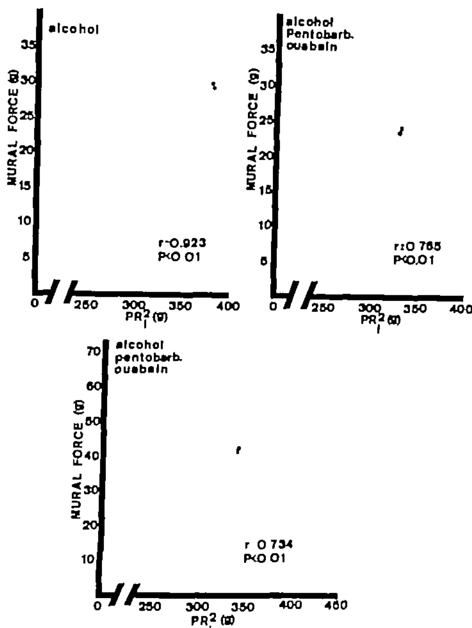


Fig 6 Data obtained from three separate experiments yield a highly significant correlation of mural force (MF) with distending force, PR^2 Determ nations were made at varying intervals during and following drug infusion All measurements were taken at peak MF (the end of isovolumic contraction) r = Correlation coefficient p = probability PR_i^2 = product of left ventricular pressure and the square of the internal radial index.

In this present study the load on the heart, and changes in CF were assessed by strain-gauge techniques In these ex periments MI measured with the Hefner gauge was used as a directly recorded index of the load since measurements with this gauge have been shown to correlate with PR^2 the total force in grams at the equator of the ventricle[7,10] Measurements of CF with the Walton Brodie arch reflect changes in contractile processes as influenced by neurogenic and chemical means and are relatively uninfluenced by changes in heart size or arterial blood pressure[11] Changes in CF occurring in the myocardial segment subtended by this arch have been shown to represent homogeneous CF changes in the surrounding myocardium[11] These mea surements of CF since length is fixed cannot reflect changes in the contractile process produced by length tension rela tionship Changes in MSL an index of ventricular radius were obtained with an isotonic strain gauge and were employed to define length-dependent changes in contractility This isotonic arch has been

Effects of ventilation on pulmonary arterial flow and vascular conductance

Hiroshi Murao M.D., Ph.D
*Simon Rodbard M.D. Ph.D.***
Tokyo, Japan, and Duarte, Calif

The influence of the volume of inflation of the lung on the pulmonary vascular conductance (flow rate/arteriovenous pressure difference, i.e., resistance⁻¹) has long been in controversy. Burton and Patel reported that positive pressure inflation of the collapsed lung by the addition of discrete volume increments caused the pulmonary vascular conductance to rise from very low values, level off in the middle range of inflation and then decline when excessive lung volumes were approached. On negative pressure inflation, they found only a slight increase in pulmonary vascular conductance. Thomas, Griffo, and Roos[2] using negative pressure inflation found the type of change that Burton and Patel had reported for positive pressure inflation. On the basis of such data, Mead and Whittenberger[3] concluded that ventilation probably had only minimal effects on pulmonary vascular conductance in natural breathing, i.e., by changes in pleural pressure. This conclusion was based on the belief that the alveolar pressure was essentially equal to atmospheric pressure.

Our laboratory has previously examined the direct effects of ventilation on airway pressure and the resulting indirect effects on transmural capillary pressures and thereby on pulmonary vascular conductance.[7]

The present study examines the dynamic effect of ventilation produced by pleural pressure changes on the pulmonary arterial flow and vascular conductance.

Methods

Dogs, weighing 12 to 30 kilograms were anesthetized with intravenous pentobarbital sodium solution (25 mg. per kilogram). After tracheal cannulation and left thoracotomy, positive pressure ventilation with 100 per cent oxygen for 15 minutes washed the gaseous nitrogen out of the lung. The airway was then clamped. The continuing blood flow absorbed the oxygen in the lobe and the lung lobe collapsed.[8] Heparin (1 mg. per kilogram) was given intravenously. Cannulas were tied into the airway, pulmonary artery, and vein of the excised left lower lobe. Blood remaining in

From the Department of Cardiology and Cardiac Research, Division of Medicine, City of Hope Medical Center, Duarte, Calif.
Supported in part by Grant HE 09721 from the National Institutes of Health of the United States Public Health Service and Grant 398 from the Los Angeles County Heart Association, Los Angeles, Calif.
Received for publication March 9, 1970.
Reprint requests to: Simon Rodbard, M.D., City of Hope Medical Center, Duarte, Calif. 91010.
*Advanced Research Fellow, Los Angeles County Heart Association (1967 to 1968). Present address: University of Tokyo School of Medicine, Tokyo, Japan.
**Director, Department of Cardiology and Cardiac Research, City of Hope Medical Center, Duarte, Calif.

tricle with a given CF developed per beat

The cardiac dilation and depression induced by alcohol may be an important factor in explaining the diminished ability of an intoxicated individual to respond normally to sudden hemodynamic stress. Further sudden stress to the cardiovascular system such as acute blood loss with decreased O_2 delivery or rapid transfusion might well be the final factor that could place cardiac function on the descending limb of the Starling curve.

Summary

Anesthetized open-chest dogs were employed to examine the depressed ventricular dynamics produced by infusions of alcohol and pentobarbital and reversal of this depression with ouabain. Changes in left ventricular contractility, size and loading conditions (mural force) were continuously monitored with strain gauges. Measurements made from these strain gauge recordings indicate that the ventricle depressed with alcohol operates under increased load. Moreover, compensation for this increased load is through the limited Frank-Starling mechanism. Essentially similar results were obtained with pentobarbital infusions. Infusion of ouabain reversed the depressions, i.e., contractility was increased while mural force and ventricular size decreased. Such findings described the precarious state of ventricular function at moderate blood alcohol levels and may account for the lability of acutely intoxicated patients to hemodynamic stress.

We wish to acknowledge the cooperation of Dr. Richard H. Gadsden, Department of Chemistry in determining blood alcohol levels.

REFERENCES

1. Cournand A.: Shock and circulatory homeostasis, Trans. Fourth Conference on Shock, Josiah Macy Jr. Foundation, Madison, N. J., 1955, p. 90.
2. Moss, L. K., Chenault, O. W., Jr., and Gaston, E. A., Jr.: The effects of alcohol ingestion on experimental hemorrhagic shock, Surg. Forum 10:390, 1959.
3. Knott, D. H., and Beard, J. D.: The effects of chronic ethanol administration on the response of the dog to repeated acute hemorrhages, Amer. J. Med. Sci. 254:178, 1967.
4. Webb, W. R., Degerli, I. U., Cook, W. A., and Unal, M. D.: Alcohol, digitalis, and cortisol and myocardial capacity in dogs, Ann. Surg. 163:811, 1966.
5. Regan, T. J., Koroxenidis, G., Moschos, C. B., Oldewurtel, H. A., Lehan, P. H., and Hellems, H. K.: The acute metabolic and hemodynamic responses of the left ventricle to ethanol, J. Clin. Invest. 45:270, 1966.
6. Braunwald, E., Ross, J., Jr., Gault, J. H., Mason, D. T., Mills, C., Gabe, I. T., and Epstein, S. E.: Assessment of cardiac function, Ann. Intern. Med. 70:369, 1969.
7. Hefner, L. L., Sheffield, L. T., Cobb, C. G., and Klip, W.: Relation between mural force and pressure in the left ventricle in the dog, Circ. Res. 11:654, 1962.
8. Aull, J. C., and McCord, W. M.: A simple apparatus and procedure for the determination of blood alcohol, Amer. J. Clin. Path. 42:315, 1964.
9. Snedecor, G. W.: Statistical methods, ed. 5, Ames, Iowa, 1956, The Iowa State College Press.
10. Newman, W. H., and Walton, R. P.: Alterations in left ventricular dimensions and mural force following coronary occlusion, Amer. J. Physiol. 211:1388, 1966.
11. Sulzer, R.: The influence of alcohol on the isolated mammalian heart, Heart 11:141, 1924.
12. Burch, G. E., Ray, C. T., and Cronvich, J. A.: Certain mechanical peculiarities of the human cardiac pump in normal and diseased states, Circulation 5:504, 1952.
13. Gorlin, R.: Recent conceptual advances in congestive heart failure, J.A.M.A. 179:441, 1962.
14. Levine, H. J., and Wagman, R. J.: Energetics of the human heart, Amer. J. Cardiol. 9:372, 1962.
15. Cotten, M. deV.: Circulatory changes affecting measurement of heart force *in situ* with strain gauge arches, Amer. J. Physiol. 174:365, 1953.
16. Reeves, T. J., and Hefner, L. L.: Isometric contraction and contractility in the intact mammalian ventricle, Amer. Heart J. 64:525, 1962.
17. Newman, W. H., and Walton, R. P.: Strain gauge arch recordings from an acutely ischemic area of the left ventricle, J. Appl. Physiol. 23:398, 1967.
18. Cotten, M. deV., and Maling, J. M.: Relationships among stroke work, contractile force and fiber length during changes in ventricular function, Amer. J. Physiol. 189:580, 1957.

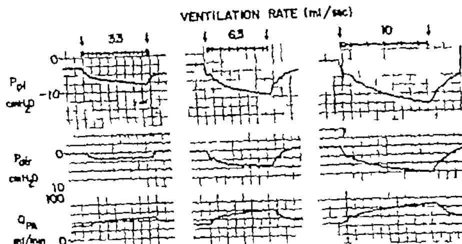


Fig. 2 Inflation rate. Three successive experiments in the same lung are shown from left to right. Data in each column were recorded simultaneously. At the top of each column, one-second time markings are indicated. The figure above the interval noted by each pair of arrows is the flow rate (ml/sec) produced by the pump. A total of 50 ml was displaced in each inflation. The top row of tracings shows the pleural pressure in centimeters of H_2O. During inflation, P_{pl} falls. The extent of this fall varies with the inflation rate. Initially airway pressure, P_{air} (middle row) was 3 cm. of H_2O higher than pleural pressure. The fall in P_{air} noted on inflation is more marked at rapid ventilation rates. Flow into the pulmonary artery Q (lowest row) increases with inflation rate.

The effects of injections of 1 ml. of RL containing either acetylcholine chloride (0.03 to 1 µg per gram of lobe) or histamine acid phosphate (0.2 to 10 µg per gram of lobe) into the RL entering the pulmonary artery were also recorded.

Pulmonary vascular conductance was calculated as the flow rate into the pulmonary artery per minute divided by the difference between the pulmonary arterial and venous pressures.

Airway conductance was calculated as the rate of flow produced by the pump connected to the pleural compartment, divided by the difference between pleural and airway pressures.

Results

1 Rate of change of lobar volume Flow into the pulmonary artery increased during inflation of the lobe (Fig 2) and decreased during deflation (Fig 3) These effects varied with the rate of change of lobar volume (Figs. 2 and 3) The deviation of the pulmonary arterial flow rate from the control (nonventilated) flow rate for each rate of lobar volume change was greater during deflation than during inflation (Fig. 4)

During inflation the pressures in the pleural and in the airway compartments fell with a constant volume per unit of time. These changes varied with the rate of lobe inflation or deflation.

Similar results were obtained when the lobar volume changes were produced with a sinusoidal pump. Thus, Fig 5 shows the effect of ventilation rates of 1 1.5 and 2 cycles per minute on the simultaneous pressures in the pleural space and in the airway and on the rate of inflow into the pulmonary artery As the rate of ventilation was increased, the rises in pleural and airway pressures during deflation of the lobe were somewhat larger than the falls in these pressures during inflation. Calculations show that as the number of cycles of ventilation per minute is increased the mean vascular conductance decreases significantly (Fig 6)

2 Bronchoconstrictors In these sets of experiments, the rate of inflation or deflation of lobar volume was maintained constant at 2.5 ml. per second for 20 seconds, for a total of 50 ml. The observed changes in the arterial inflow rate varied with the quantity of acetylcholine administered into the pulmonary artery (Figs. 7 and 8) Acetylcholine accentuated the changes pro-

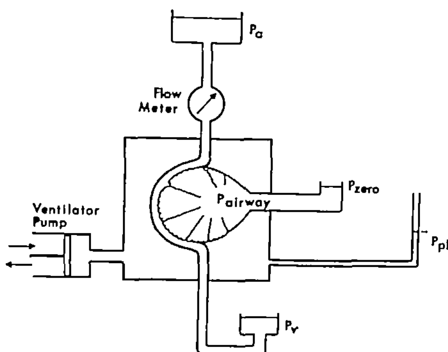


Fig *1* The preparation. An air free lung lobe (scalloped edges) prepared as described in text, is introduced into a rigid (pleural) container (stippled square) consisting of a glass bottle. The pleural pressure in the container is measured by a manometer (P_{pl} at right) A ventilator pump (at left) introduces or withdraws Ringer Locke solution (*RL*) into or out of the pleural container at selected rates. This change in container volume produces an equal change in lung lobe volume Overflow arrangements' (not shown) prevent the entrance of air into the system. A reservoir at height P delivers RL through an electromagnetic flowmeter into the pulmonary artery the outflow enters a constant level reservoir P_v. Pressures in the airway (P_{airway}) and in the pleural space (P_{pl}) were monitored with Statham strain-gauge manometers (P23G) on a direct writing Sanborn chart recorder

the pulmonary vessels was washed out by perfusion with Ringer Locke solution (RL)

The lobe was suspended in a pleural compartment consisting of an RL filled glass bottle (Fig 1) A constant pressure arterial reservoir (P) produced flow of RL through the pulmonary vascular bed to a constant level venous pressure reservoir (P) Airway and pleural compartments were each connected to separate constant level reservoirs. Placement of the pleural fluid reservoir at a selected distance below the airway reservoir permitted the lobe to fill with RL in accordance with lobe compliance (volume/pressure) An electromagnetic flowmeter probe registered the flow into the pulmonary artery

The connection between the pleural compartment and its reservoir was then clamped Ventilation was simulated by displacing fluid into and out of the pleural space at a constant rate or with a sinusoidal pump Fluid displacement rates were arranged so that conditions arising in the liquid ventilated lung were dimensionally equivalent to those in the air ventilated lung (see Appendix)

The zero pressure reference was the anatomical level of the hilum Pressures in the pleural (P_{pl}) and airway (P_{airway}) compartments were recorded together with the rate of flow into the pulmonary artery ($\dot{Q}_{PA}$) The effects of the rate of change of lobar volume on these values were examined at several selected rates of volume displacement. The estimated normal tidal volume of the left lower lobe of the dog (50 ml) was introduced into or withdrawn from the pleural compartment in the course of intervals ranging from 5 to 60 seconds. Because of the incompressibility of the liquid system these maneuvers produced equivalent volume changes in the lung lobe. The Reynolds numbers (see Appendix) for the flow rates of RL into and out of the lobe were set at values calculated for equivalent tidal volumes of air ventilation at frequencies of 6 to 76 cycles per minute.

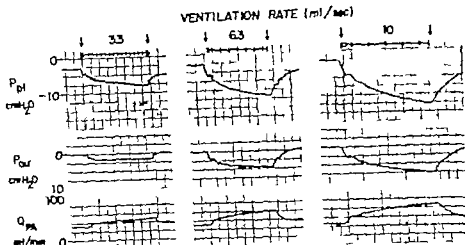


Fig 2 Inflation rate. Three successive experiments in the same lung are shown from left to right. Data in each column were recorded simultaneously At the top of each column, one-second time markings are indicated. The figure above the interval noted by each pair of arrows is the flow rate (ml/sec) produced by the pump. A total of 50 ml was displaced in each inflation. The top row of tracings shows the pleural pressure in centimeters of H_2O During inflation, P_{pl} falls. The extent of this fall varies with the inflation rate. Initially airway pressure, P_{aw} (middle row) was 3 cm. of H_2O higher than pleural pressure. The fall in P_{aw} noted on inflation is more marked at rapid ventilation rates. Flow into the pulmonary artery $\dot{Q}_P$ (lowest row) increases with inflation rate.

The effects of injections of 1 ml. of RL containing either acetylcholine chloride (0.03 to 1 μg per gram of lobe) or histamine acid phosphate (0.2 to 10 μg per gram of lobe) into the RL entering the pulmonary artery were also recorded.

Pulmonary vascular conductance was calculated as the flow rate into the pulmonary artery per minute divided by the difference between the pulmonary arterial and venous pressures.

Airway conductance was calculated as the rate of flow produced by the pump connected to the pleural compartment, divided by the difference between pleural and airway pressures.

Results

1 Rate of change of lobar volume Flow into the pulmonary artery increased during inflation of the lobe (Fig 2) and decreased during deflation (Fig 3) These effects varied with the rate of change of lobar volume (Figs. 2 and 3) The deviation of the pulmonary arterial flow rate from the control (nonventilated) flow rate for each rate of lobar volume change was greater during deflation than during inflation (Fig 4)

During inflation the pressures in the pleural and in the airway compartments fell with a constant volume per unit of time. These changes varied with the rate of lobe inflation or deflation.

Similar results were obtained when the lobar volume changes were produced with a sinusoidal pump Thus, Fig 5 shows the effect of ventilation rates of 1 1.5 and 2 cycles per minute on the simultaneous pressures in the pleural space and in the airway and on the rate of inflow into the pulmonary artery As the rate of ventilation was increased the rises in pleural and airway pressures during deflation of the lobe were somewhat larger than the falls in these pressures during inflation. Calculations show that as the number of cycles of ventilation per minute is increased the mean vascular conductance decreases significantly (Fig 6)

2 Bronchoconstrictors In these sets of experiments, the rate of inflation or deflation of lobar volume was maintained constant at 2.5 ml. per second for 20 seconds, for a total of 50 ml. The observed changes in the arterial inflow rate varied with the quantity of acetylcholine administered into the pulmonary artery (Figs. 7 and 8) Acetylcholine accentuated the changes pro-

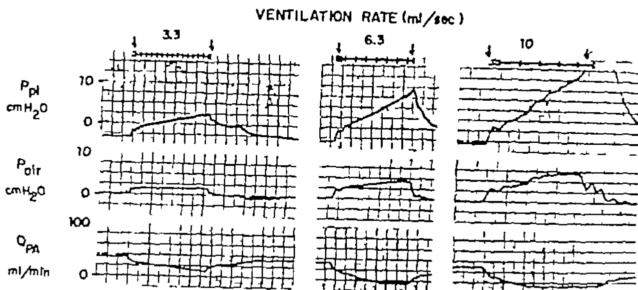


Fig 3 Deflation rate These data were collected in the same lung as the data in Fig 2 P_{pl} and P_{al} rise and $\dot{Q}_{PA}$ falls during deflation These effects increase in magnitude with the deflation rate.

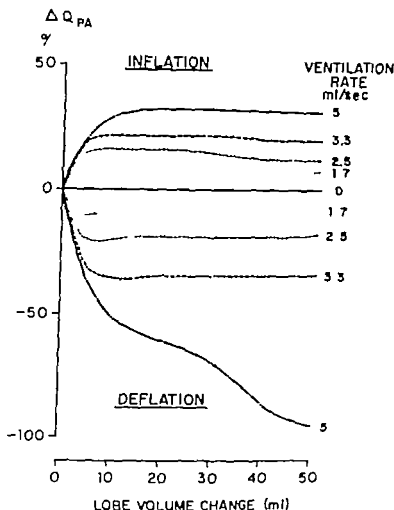


Fig. 4 Effect of ventilation rate on pulmonary arterial flow The horizontal axis gives the change i volume of the lobe in milliliters as a total of 50 ml. is introduced into or withdrawn from the pleural compartment. The vertical axis gives the percentage change in the rate of pulmonary arterial inflow during inflation and deflation, compared to the arteri l inflow when the lobe volume was held constant (heavy horizontal line) Ventilation rates (*ml/sec*) are noted on the right Arterial inflow rises with the rate of inflation of the lung lobe, and falls with the rate of deflation.

VENTILATION RATE (cycle/min)

1 1.5 2

10– 0– H_2O

10 0 P_{alv} H_2O

100 0 /min

1 min 1 min 1 min

Fig. 5 Ventilation rates, sinusoidal pump. Results are given for 1, 1.5, and 2 ventilation cycles per minute. Conventions as in Fig. 2.

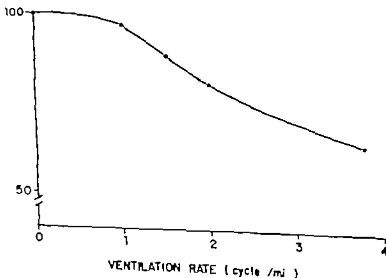


Fig. 6 Effect of ventilation rate on per cent change in mean pulmonary vascular conductance. Discussed in text.

Amer Heart J
January, 1971

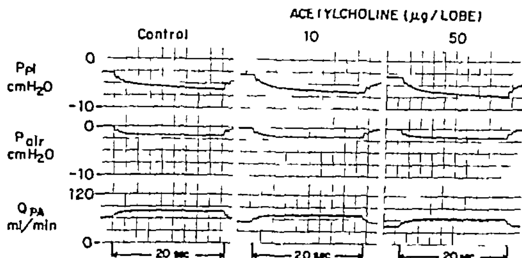


Fig 7 Acetylch line inflation phase The ventilation rate was 2.5 ml per second (50 mL in 20 sec.) for the three experiment shown Other convent ons a in Fig 2 Control record ngs are shown in the left column. At the onset of inflation P_{pl} and P_{air} f ll uddenly w th cessation of inflation, both return toward control values Arterial flow incre ses with onset of inflation and decreases at offset Acetylcholine 10 or 50 μg per lobe, injected into the arterial y tem during the phase of no ventilation, produced a small fall in P_{pl} and a fall in $\dot{Q}_{A}$ but had no effect on the P recording On inflation in accordance with the dose given, acetylcholine produced a gre ter f ll in P_{pl} and $\dot{Q}_{P}$

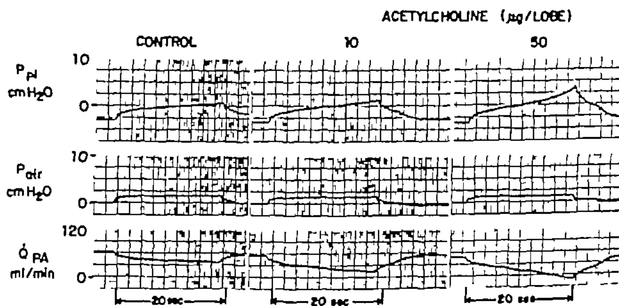


Fig 8 Acetylcholine deflation phase Prior to deflation the findings are a in Fig 6 (so lu g) On deflation P_{pl} and $\dot{Q}_{PA}$ responses were greater with acetylchol ne These effects were dose-depende t P was not ffected

duced by deflation and infl tion on the pleural pressure response (Figs. 7 and 8) and on the arterial inflow rate (Figs. 7 to 9) No effect was seen on the recorded airway pressure response to ventilation The results were similar when a sinusoidal pump was used to deflate and inflate the lung (Fig 10) Essentially similar results were ob tained with histamine (Fig 11)

Discussion

Our data demonstrate that the pul monary vascular conductance calculated from the pulmonary arterial inflow rate varies during ventilation with the direc tion and rate of change of volume of the lobe

As a falling pleural pressure inflates the lobe alveolar pressure must also fall Our

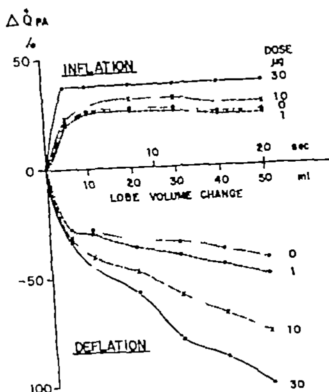


Fig. 9 Effect of acetylcholine on pulmonary arterial flow. The horizontal axis gives the change of lobe volume and the time in which this was accomplished for total of 50 ml. in 20 sec. The percentage change in pulmonary arterial flow is given on the ertical axis ($\dot{Q}_{PA}$). Acetylcholine dosages (indicated t right) were 0, 1 10, or 30 μg per lobe.

measurements of airway pressure do not provide a measurement of alveolar pressure since the cannula in the airway could only measure the pressure in the large airway. However the magnitude of the decline in alveolar pressure can be expected to vary directly with the rate at which the lobar volume is being expanded and inversely with the conductance of the airways. Since the arteriovenous pressure difference was held constant in the present preparation pulmonary intracapillary pressure must also remain relatively constant. The transmural (intravascular-extravascular) pressure in such intralobar capillaries will therefore vary inversely with the alveolar pressure. During inflation the fall in alveolar pressure raises the capillary transmural pressure and thus tends to open previously collapsed alveolar capillaries. The pulmonary vascular conductance can be expected to vary with the caliber of the pulmonary capillaries.

Conversely an acute rise in pleural pressure decreases the volume of the lung and increases the alveolar pressure. The resulting lowering of the capillary transmural pressure tends to collapse the alveolar capillaries and thereby to decrease their vascular conductance.

The foregoing description of the dynamically ventilated lung indicates that the instantaneous pulmonary vascular conductance is affected by the direction and the rate of change of lobar volume, and by the inverse of airway conductance. These effects are absent when the volume of the lung is held constant,[3] since alveolar pressure equilibrates rapidly with ambient pressure and the capillary pressure is maintained at a constant value. As a result, the pulmonary vascular conductance in the non

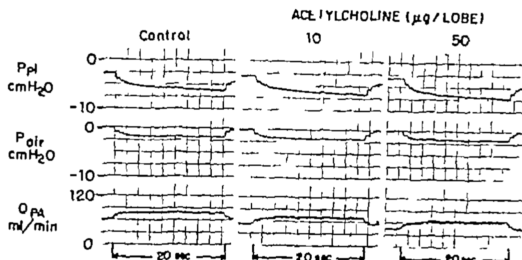


Fig 7 Acetylcholine inflation phase The ventilation rate was 2.5 ml per second (50 ml in 20 sec.) for the three experiment shown Other conventions a in Fig 2. Control recordings are shown n the left column. At the onset of nflation P_{pl} and P fall uddenly with cessation of inflation, both return toward control values. Arterial flow increases w th onset of inflation and decreases at offset. Acetylcholine 10 or 50 µg per lobe, injected nto the arterial ystem during the phase of no ventilation, produced a small fall in P_{pl} and a fall in $\dot{Q}_{PA}$ but had no effect on the P_{air} record ng On inflat on n accordance with the dose given, acetylcholine produced a greater f ll in P_{pl} and $\dot{Q}_{PA}$

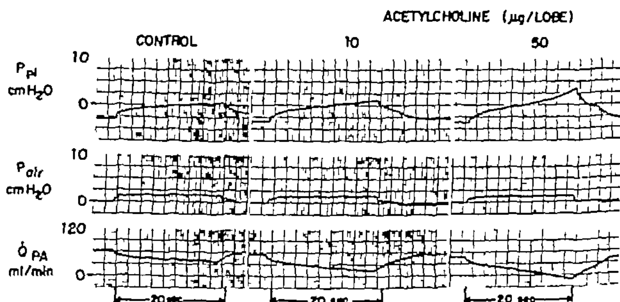


Fig. 8 Acetylchol ne deflation ph se Prior to deflation the find ngs are as in F g 6 (sa l ng) On deflation P_{pl} and $\dot{Q}_{PA}$ responses were greater with acetylchol ne These effects were dose-dependent. P was not ffected

duced by deflation and inflation on the pleural pressure response (Figs. 7 and 8) and on the arterial inflow rate (Figs 7 to 9) No effect was seen on the recorded airway pressure response to ventilation The results were similar when a sinusoidal pump was used to deflate and inflate the lung (Fig 10) Essentially similar results were obtained with histamine (Fig 11)

Discussion

Our data demonstrate that the pulmonary vascular conductance calculated from the pulmonary arterial inflow rate varies during ventilation with the direction and rate of change of volume of the lobe

As a falling pleural pressure inflates the lobe alveolar pressure must also fall Our

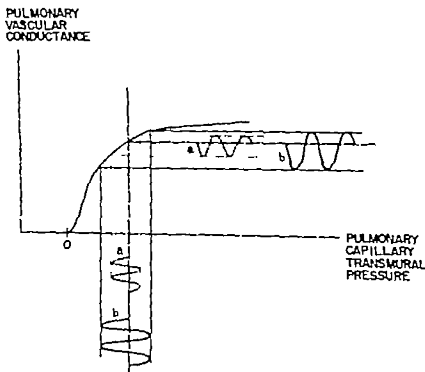


Fig. 12. Analysis of the effects of ventilation. Horizontal axis indicates the pulmonary capillary transmural pressure vertical axis indicates the pulmonary vascular conductance. The heavy curved line beginning at zero is taken from previous publication. The projections indicate that entilatory oscillations modify the capillary transmural pressure and, through this, the pulmonary vascular conductance. Effects produced by small oscillations are indicated t effects produced by larger oscillations are indicated at *b*

increase during inflation. This difference in magnitudes varies with (1) the rate of change of lobe volume (Figs. 2 to 5) and (2) with the degree of bronchoconstriction (Figs. 7 to 11)

The results obtained with sinusoidal ventilation of the lobe show that the *mean* vascular conductance declines as the frequency of ventilation increases (Fig 6) These data demonstrate a profound effect of ventilation not only on the instantaneous, but also on the mean vascular conductance. These effects appear to operate through the limitations in distensibility of the pulmonary capillary bed (Fig 12)

Vascular conductance falls toward zero as negative transmural (intralobar-intracapillary) pressure collapses the alveolar capillaries (Fig. 12) As capillary transmural pressure rises above zero the alveolar capillaries begin to open and the vascular conductance increases in a nonlinear manner Vascular conductance becomes maximal at a positive transmural pressure of about 5 cm. of H_2O [7] Further increments of intramural capillary pressure up to about 14 cm. of H_2O have only minimal effects on the caliber of the pulmonary capillaries, and thus on pulmonary vascular conductance.

Both the nonlinearity of the effects of transmural pressure on conductance and the asymmetrical changes of alveolar pressure during inflation or deflation of the lobe contribute to the determination of the ventilatory changes in the mean pulmonary vascular conductance.

The foregoing findings may have relevance in the interpretation of clinical data. The well-documented rise in pulmonary arterial pressure in obstructive lung disease has been attributed variously to hypoxia or acidosis. The present studies suggest that the rise in pulmonary arterial pressure

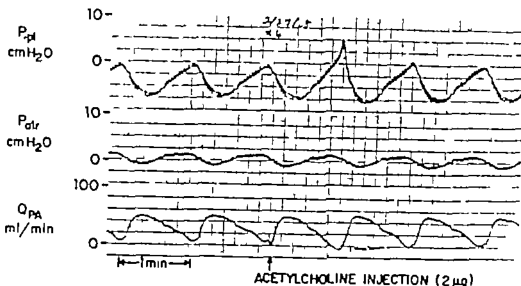


Fig *10* Acetylcholine njection Sinusoidal ventilation Conventions as in Fig 2 Discussed in text.

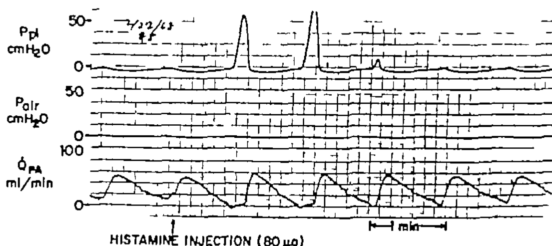


Fig *11* Histamine njectio Si usoidal ventilation Conventions as Fig 2 Discussed in text.

ventilated lung is relatively constant regardless of the extent to which it is filled provided it is neither collapsed nor hyper inflated

The magnitude of the decrease in the pulmonary vascular conductance was greater during deflation than the increase during inflation (Fig 4) The difference between deflation and inflation also varied with the rate of change of lobar volume (Fig 4)

The difference between the changes in vascular conductance of the lobe during inflation (Figs. 2 4 and 5) and those during deflation (Figs. 3 4 and 5) may represent (a) phasic differences in airway conductance or (b) nonlinear effects of transmural capillary pressure on vascular conductance (Fig 12)

During deflation the pressure changes generated in the pleural space and in the airway are greater than the pressure changes during inflation (Fig 13) Inflation and deflation must therefore produce unsymmetrical effects on alveolar pressure and through these generate unsymmetrical changes in pulmonary vascular conductance.

Vascular conductance varies from moment to moment in the ventilating lung As noted the magnitude of the decrease in the vascular conductance during deflation is larger than the magnitude of the

vascular conductance were examined in the isolated lung lobe of the dog. The lobe was suspended in, filled with and perfused with Ringer Locke solution at selected constant pressures. Ventilation was produced by displacement of fluid into and out of the "pleural" space surrounding the lobe. During inflation of the lobe the inflow rate decreased. The magnitude of the changes in the pulmonary arterial flow varied directly with the rate of change of volume of the lobe, and inversely with the conductance of the airways. For a given airway conductance or rate of change of lobar volume, the magnitude of the change in pulmonary arterial flow during deflation was greater than the magnitude of the change during inflation. These effects were augmented by the administration of acetylcholine or histamine.

The results show that airway conductance and the rate of lobar volume change can significantly affect flow into the pulmonary artery and the mean pulmonary vascular conductance. These effects apparently result from changes in alveolar and transmural capillary pressures. The results also suggest that acetylcholine and histamine act directly on the bronchial smooth muscle, and thereby indirectly on the pulmonary vessels by raising alveolar pressure during deflation of the lung. The elevated alveolar pressure tends to collapse the pulmonary capillaries and thereby to reduce the pulmonary vascular conductance.

REFERENCES

1. Burton, A. C., and Patel, D. J.: Effect on pulmonary vascular resistance of inflation of the rabbit lungs, J. Appl. Physiol. 12:239, 1958.
2. Thomas, L. J., Jr., Griffo, Z. T., and Roos, A.: Effect of negative-pressure inflation of the lung on pulmonary vascular resistance, J. Appl. Physiol. 16:451, 1961.
3. Mead, J., and Whittenberger, J. L.: Lung inflation and hemodynamics, Fenn, W. O., and Rahn, H., editors: Handbook of physiology, section 3, Respiration, vol. 1, Washington, D. C., 1964, American Physiological Society, pp. 477-486.
4. Rodbard, S.: Bronchomotor tone. A neglected factor in the regulation of the pulmonary circulation, Amer. J. Med. 15:356, 1953.
5. Harasawa, M., and Rodbard, S.: The effects on pulmonary vascular resistance of inflation, transpulmonary air pressure and pulmonary venous pressure, Cardiologia 39:215, 1961.
6. Kira, S., and Rodbard, S.: Pulmonary vascular compliances and filtration, Amer. Heart J. 71:371, 1966.
7. Rodbard, S., and Kira, S.: Mechanical forces and pulmonary vascular conductance, Amer. Heart J. 72:498, 1966.
8. Corylllos, P. N., and Birnbaum, G. L.: Studies in pulmonary gas absorption in bronchial obstruction, Amer. J. Med. Sci. 183:317, 1932.
9. Barer, G. R., and McCurrie, J. R.: Pulmonary vasometer responsible in the cat: the effects and interrelationships of drugs, hypoxia and hypercapnia, Quart. J. Exp. Physiol. 54:156, 1969.
10. Rose, J. C.: Active constriction and dilatation in pulmonary circulation in response to acetylcholine, Proc. Soc. Exp. Biol. Med. 94:734, 1957.

Appendix

The dynamic conditions in which two apparently different but geometrically similar systems are equivalent to each other are stated by the law of similitude for fluid dynamics. Similitude is present when two systems have the same Reynolds number. If the Reynolds number for a lung lobe ventilated with RL is the same as when it is ventilated with air, the dynamic conditions of the two systems can be regarded as equivalent.

This condition is fulfilled when

$$\frac{\text{diameter of the airway} \times \text{velocity of the flow of RL}}{\text{kinematic viscosity of RL}} = \frac{\text{diameter of the airway} \times \text{velocity of the flow of air}}{\text{kinematic viscosity of air}}$$

Since the airways and their diameters are identical in the present case, this yields

$$\frac{\text{velocity of flow of RL}}{\text{velocity of flow of air}} = \frac{\text{kinematic viscosity of RL}}{\text{kinematic viscosity of air}}$$

At 15° C., the kinematic viscosity of air is 0.145 sq. cm. per second and the kinematic viscosity of water is 0.0114 sq. cm. per second. Thus, an air flow velocity of 12.7 cm. per second produces the same effects as a water flow velocity of 1 cm. per second.

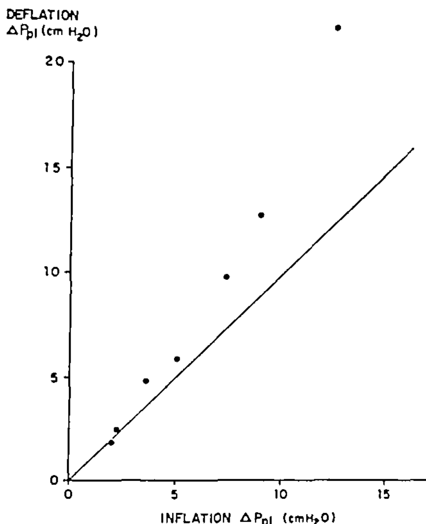


Fig 13 Comparison of cha ges n pleural pressure during inflation and deflation. Horizontal axis gives change of pleural pressure during inflation vertical axis gives cha ge during deflation. The poi ts represent values after a change of 50 ml in lu g lobe volume. The line of identity is hown. Deviat on of the points from this line indicate that the changes dur g deflation exceed those during inflation.

may be accounted for at least in part by the changes in pulmonary vascular con ductance which result from an increased rate of ventilation or a decreased airway conductance.

The decrease in pulmonary vascular con ductance following the administration of acetylcholine or histamine has generally been attributed to a direct effect of these drugs on the pulmonary blood vessels[19] If these agents acted directly on the blood vessels, vascular conductance would be diminished in both the inflation and defla tion phases of ventilation However Figs. 7 to 11 show that these agents not only cause a reduction in arterial flow during deflation but they also cause a slight in crease in arterial flow during inflation These effects were dose-dependent Since the arteriovenous pressure difference was held constant the changes in flow represent equivalent changes in conductance. These findings support the thesis that these drugs act on the bronchial smooth muscle rather than directly on the vascular smooth muscle

The present data and analysis show that the tone of the bronchial musculature and the rate of change of lung volume during ventilation can produce indirect but very significant effects on pulmonary vascular conductance A role for bronchomotor tone in the regulation of pulmonary vascular dynamics is thus indicated

Summary

The effects of the direction and of the rate of change of lung volume on the pulmonary

vascular conductance were examined in the isolated lung lobe of the dog. The lobe was suspended in, filled with, and perfused with Ringer Locke solution at selected constant pressures. Ventilation was produced by displacement of fluid into and out of the pleural space surrounding the lobe. During inflation of the lobe the inflow rate decreased. The magnitude of the changes in the pulmonary arterial flow varied directly with the rate of change of volume of the lobe and inversely with the conductance of the airways. For a given airway conductance or rate of change of lobar volume, the magnitude of the change in pulmonary arterial flow during deflation was greater than the magnitude of the change during inflation. These effects were augmented by the administration of acetylcholine or histamine.

The results show that airway conductance and the rate of lobar volume change can significantly affect flow into the pulmonary artery and the mean pulmonary vascular conductance. These effects apparently result from changes in alveolar and transmural capillary pressures. The results also suggest that acetylcholine and histamine act directly on the bronchial smooth muscle, and thereby indirectly on the pulmonary vessels by raising alveolar pressure during deflation of the lung. The elevated alveolar pressure tends to collapse the pulmonary capillaries and thereby to reduce the pulmonary vascular conductance.

REFERENCES

1. Burton, A. C., and Patel, D. J.: Effect on pulmonary vascular resistance of inflation of the rabbit lungs, J. Appl. Physiol. 12:239, 1958.
2. Thomas, L. J., Jr., Griffo, Z. T., and Roos, A.: Effect of negative-pressure inflation of the lung on pulmonary vascular resistance, J. Appl. Physiol. 16:451, 1961.
3. Mead, J., and Whittenberger, J. L.: Lung inflation and hemodynamics, in Fenn, W. O., and Rahn, H., editors: Handbook of physiology, section 3: Respiration, vol. 1, Washington, D. C., 1964, American Physiological Society, pp. 477-486.
4. Rodbard, S.: Bronchomotor tone. A neglected factor in the regulation of the pulmonary circulation, Amer. J. Med. 15:356, 1953.
5. Harasawa, M., and Rodbard, S.: The effects on pulmonary vascular resistance of inflation, transpulmonary air pressure and pulmonary venous pressure, Cardiologia 39:245, 1961.
6. Kira, S., and Rodbard, S.: Pulmonary vascular compliances and filtrations, Amer. Heart J. 71:371, 1966.
7. Rodbard, S., and Kira, S.: Mechanical forces and pulmonary vascular conductance, Amer. Heart J. 72:196, 1966.
8. Coryllos, P. N., and Birnbaum, G. L.: Studies in pulmonary gas absorption in bronchial obstruction, Amer. J. Med. Sci. 183:317, 1932.
9. Barer, G. R., and McCurrie, J. R.: Pulmonary vasomotor responsible in the cat; the effects and interrelationships of drugs, hypoxia and hypercapnia, Quart. J. Exp. Physiol. 54:156, 1969.
10. Rose, J. C.: Active constriction and dilatation in pulmonary circulation in response to acetylcholine, Proc. Soc. Exp. Biol. Med. 94:734, 1957.

Appendix

The dynamic conditions in which two apparently different but geometrically similar systems are equivalent to each other are stated by the law of similitude for fluid dynamics. Similitude is present when two systems have the same Reynolds number. If the Reynolds number for a lung lobe ventilated with RL is the same as when it is ventilated with air, the dynamic conditions of the two systems can be regarded as equivalent.

This condition is fulfilled when

$$\frac{\text{diameter of the airway} \times \text{velocity of the flow of RL}}{\text{kinematic viscosity of RL}} = \frac{\text{diameter of the airway} \times \text{velocity of the flow of air}}{\text{kinematic viscosity of air}}$$

Since the airways and their diameters are identical in the present case, this yields

$$\frac{\text{velocity of flow of RL}}{\text{velocity of flow of air}} = \frac{\text{kinematic viscosity of RL}}{\text{kinematic viscosity of air}}$$

At 15° C., the kinematic viscosity of air is 0.145 sq. cm. per second and the kinematic viscosity of water is 0.0114 sq. cm. per second. Thus, an air flow velocity of 12.7 cm. per second produces the same effects as a water flow velocity of 1 cm. per second.

Sequential effect of angiographic contrast agent on canine renal and systemic hemodynamics

George A. Porter, M.D.
Frank E. Kloster, M.D.
J. David Bristow, M.D.
Portland, Ore.

We have previously studied the immediate hemodynamic effect which follows cardiac injection of angiographic contrast solutions in man and animals.[1-3] During the course of these investigations we became interested in the diuresis which regularly follows the injection of 80 per cent sodium iothalamate (Angio-Conray, Mallinckrodt). To quantitate the magnitude and hemodynamic consequences of the diuresis we have made sequential measurements of systemic and renal hemodynamics in dogs during the diuresis produced by iothalamate and compared it to hypertonic mannitol. In addition, we have characterized the manner in which iothalamate is excreted by the dog.

Methods

Twenty-four dogs were lightly anesthetized with sodium pentobarbital (25 mg. per kilogram); their weights varied from 13 to 23 kilograms. Catheterization of the left ventricle was accomplished by passing a 7 Fr. catheter retrogradely from the right superficial femoral artery, while the left femoral artery was cannulated with a polyethylene catheter, 15 cm. in length having an internal diameter of 0.11 cm. Blood for dye-dilution curves was sampled in a Colson densitometer after being drawn from the polyethylene catheter at a rate of 24.7 ml. per minute. Indocyanine green was injected through a 7 Fr. catheter that had been positioned in the inferior vena cava, being introduced from the right femoral vein. The left brachial artery and vein were each cannulated with polyethylene tubing 15 cm. in length. The arterial cannula was used for measuring systemic arterial pressure through a Statham P23D strain gauge, while the venous cannula was used to administer a 2 ml. per minute infusion of para-aminohippurate (PAH) and inulin solution. Recordings were made by a Gilson direct writing oscillograph.

All animals were in a fasting state for 12 hr. prior to experimental manipulation. During surgical preparation a 2 ml. per minute infusion of normal saline was provided to establish a satisfactory urine flow. Through a midline incision in the lower abdomen both ureters were isolated 4 to 5 cm. above the vesicoureteral junction. PE 240 polyethylene tubing, 25 cm. in

From the Division of Cardiovascular Renal Disease, Department of Medicine, University of Oregon Medical School, Portland, Ore.

This investigation was supported in part by the CV Program Project Grant HE 06336-08.
Received for publication March 16, 1970.

Reprint requests to: George A. Porter, M.D., Department of Medicine, University of Oregon Medical School, Portland, Ore. 97201

January 1971 Vol. 81 No. 1 80-92

length was introduced into each ureter and advanced into the renal pelvis. The abdomen was closed and both catheters were brought through the incision to collection bottles.

One of 3 different materials was injected into the left ventricle in each animal. Normal saline was used in the 5 control animals and was given as a volume equal on a body weight basis to the amount of sodium iothalamate given to other dogs, i.e. 0.5 ml. per kilogram. Twenty-five per cent mannitol was given in an equiosmotic dose to sodium iothalamate, i.e. 0.82 ml. per kilogram.

The standard protocol follows. After collection of control blood and urine samples, priming amounts of 10 per cent inulin (0.75 ml. per kilogram) and 20 per cent para-aminohippurate (0.04 ml. per kilogram) were given intravenously followed by a 2 ml. per minute sustaining infusion of a solution of inulin and PAH calculated to maintain a plasma inulin concentration between 30 and 40 mg. per cent, and a plasma PAH concentration of 2 mg. per cent. Following on hour of equilibration three 10 minute urine collections were made and 8 ml. of arterial blood were drawn at the midpoint of each clearance. All blood samples were replaced by an equal volume of normal saline immediately after sample withdrawal. In addition, following each midpoint blood sample cardiac output was determined by injection of 2.5 mg. of indocyanine green into the inferior vena cava with sampling from the femoral artery catheter. As reported previously[3] sodium iothalamate does not interfere with the measurement of cardiac output by indocyanine green at the sampling times used in this study. The blood drawn for dye-dilution curves was immediately reinfused. After completing the three 10 minute control measurements, normal saline was injected into the left ventricle of 5 animals, 25 per cent mannitol in 8 animals, and 80 per cent sodium iothalamate into 11 animals. Left ventricular injection required 2 to 4 sec. for completion and was performed by hand. Cardiac output was determined immediately prior to ventricular injection and then 15 sec. afterward. Urine collections were closed at 5 and 15 min. after injection then at 15 minute intervals until at least 60 min. had passed. Postinjection clearance intervals were numbered consecutively from I through V. At the midpoint of each urine collection an arterial blood sample was drawn and cardiac output measured.

In two animals, urine losses following 80 per cent sodium iothalamate were replaced using an "artificial urine" composed of 0.45 per cent normal saline and 2.5 per cent glucose with 40 mEq. per liter of potassium added. Replacement rate was varied to match the difference in urine flow after sodium iothalamate as compared to the control rate. Finally in four animals 15 mc. of sodium iothalamate [131]I (Abbott Laboratories) were mixed with sufficient nonradioactive sodium iothalamate to give a final injection volume of 0.5 ml. per kilogram. Following left ventricular injection radioactivity of the urine and blood samples was measured in an automatic gamma spectrometer (Model 1085, Nuclear of Chicago). In three of the animals the renal circulation was intact, however in the fourth dog both renal arteries were cross clamped immediately before injection of the radioactive sodium iothalamate.

The hematocrit was measured by the micro-hematocrit technique and corrected for plasma trapping[4] and arterial pH was measured with a Radiometer Model 27 pH Meter. Inulin concentrations were determined by the method of Roe and associates[5] and corrected for blood glucose content. PAH was analyzed after a modification of the method of Smith and co-workers,[6] while mannitol was measured by the technique of Corcoran and Page. Osmolality was determined using a Fiske osmometer and sodium and potassium concentrations measured by a Baird flame photometer with a lithium internal standard. Chloride was quantified using the Aminco-Cotlove chloride titrator.

Calculations. Clearance rates were calculated by standard formulas. Vascular resistance was derived by dividing the mean arterial pressure by blood flow and was expressed in resistance units. For computing total systemic vascular resistance (SVR) cardiac output was the denominator and for calculating renal vascular

Sequential effect of angiographic contrast agent on canine renal and systemic hemodynamics

George A. Porter, M.D.
Frank E. Kloster, M.D.
J. David Bristow, M.D.
Portland, Ore.

We have previously studied the immediate hemodynamic effect which follows cardiac injection of angiographic contrast solutions in man and animals.[1-4] During the course of these investigations we became interested in the diuresis which regularly follows the injection of 80 per cent sodium iothalamate (Angio-Conray, Mallinckrodt). To quantitate the magnitude and hemodynamic consequences of the diuresis we have made sequential measurements of systemic and renal hemodynamics in dogs during the diuresis produced by iothalamate and compared it to hypertonic mannitol. In addition, we have characterized the manner in which iothalamate is excreted by the dog.

Methods

Twenty-four dogs were lightly anesthetized with sodium pentobarbital (25 mg. per kilogram); their weights varied from 13 to 23 kilograms. Catheterization of the left ventricle was accomplished by passing a 7 Fr. catheter retrogradely from the right superficial femoral artery, while the left femoral artery was cannulated with a polyethylene catheter, 15 cm. in length, having an internal diameter of 0.11 cm. Blood for dye-dilution curves was sampled in a Colson densitometer after being drawn from the polyethylene catheter at a rate of 24.7 ml. per minute. Indocyanine green was injected through a 7 Fr. catheter that had been positioned in the inferior vena cava, being introduced from the right femoral vein. The left brachial artery and vein were each cannulated with polyethylene tubing 15 cm. in length. The arterial cannula was used for measuring systemic arterial pressure through a Statham P23D strain gauge, while the venous cannula was used to administer a 2 ml. per minute infusion of para-aminohippurate (PAH) and inulin solution. Recordings were made by a Gilson direct-writing oscillograph.

All animals were in a fasting state for 12 hr. prior to experimental manipulation. During surgical preparation a 2 ml. per minute infusion of normal saline was provided to establish a satisfactory urine flow. Through a midline incision in the lower abdomen, both ureters were isolated 4 to 5 cm. above the vesicoureteral junction. PE 240 polyethylene tubing, 25 cm. in

From the Division of Cardiovascular Renal Disease, Department of Medicine, University of Oregon Medical School, Portland, Ore.

This investigation was supported in part by the CV Program Project Grant HE 06336-09.
Received for publication March 16, 1970.

Reprint requests to: George A. Porter, M.D., Department of Medicine, University of Oregon Medical School, Portland, Ore. 97201.

(Period V Fig 1) in animals receiving iothalamate. The decreased cardiac output at Period V in the animals given mannitol was not significant ($p > 0.1$) The late fall in cardiac output induced by the injection of sodium iothalamate was reversed in the two animals in which urine volume was replaced (Fig 2) The fall in cardiac output recorded in Period V (Fig 1) in the animals receiving sodium iothalamate was associated with a significant rise ($p < 0.05$) in both systemic vascular resistance and mean systemic blood pressure. The injection of mannitol caused a significantly decreased vascular resistance during Periods I to III while the increase noted at one hour (Period V) was also significant. Significance was determined by the "t" test for paired observations.[21]

Changes in urine volume and solute excretion following left ventricular injection of one of the three solutions Fig 3 is a plot of the sequential change in the mean rate of urine excretion, expressed per kilogram body weight, following injection of each of the three agents. The abrupt, sustained diuresis induced both by sodium iothalamate and mannitol represent a significant increase over the control interval. The integrated mean difference in urine flow between the control and postinjection period was +0.2 ml. per hour per kilogram for saline +5.5 ml. per hour per kilogram for sodium iothalamate and +2.9 ml per hour per kilogram for mannitol. Mean values for solute excretion before and after left ventricular injection were saline 2,800 ± 159 μOsm per hour per kilogram preinjection compared to 2,815 ± 374 μOsm per hour per kilogram postinjection sodium iothalamate 2,403 ± 67 μOsm per hour per kilogram preinjection versus 5,000 ± 280 μOsm per hour per kilogram postinjection and mannitol, 2,471 ± 65 μOsm per hour per kilogram preinjection versus 3,541 ± 309 postinjection.

Although the change in the rate of solute excretion following the injection of sodium iothalamate parallels the increase in urine flow rate the same is not true for the late postinjection observations in the animals given mannitol. Because of this divergence the urinary excretion of sodium, chloride nonchloride anion and nonurea nonelectrolyte solute for each of the three animal groups were tabulated and the per cent changes from the control period are plotted in Figs. 4 and 5 The mean ± S.D control values for these parameters are shown in Table II As expected the injection of sodium iothalamate was associated with a substantial increase in nonchloride anion excretion (Fig 4) since iothalamate once filtered is excreted without further modification by tubular action.[22] Furthermore the iodine of sodium iothalamate does not dissociate and therefore, does not interfere with the titration of chloride ion in the urine (Porter G A., and Kimsey J unpublished observations) Similarly mannitol a completely filterable nonreabsorbable uncharged molecule, results in a sustained increase in the nonurea, nonelectrolyte solute excretion (Fig 4) The marked

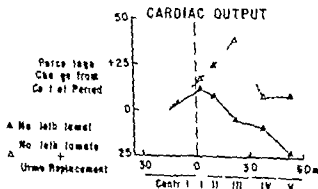


Fig. 2. Comparison of the sodium iothalamate-induced changes in cardiac output with and without replacing urine volume. Format identical to Fig. 1

resistance (RVR) renal plasma flow (C_{PAH}) was the denominator Inulin space was calculated by dividing the net inulin content of the body during any given clearance period by the plasma inulin concentration and expressing the volume as a per cent of body weight Filtered sodium and chloride were calculated using the following formula

$$F = k \quad P \quad C_I$$

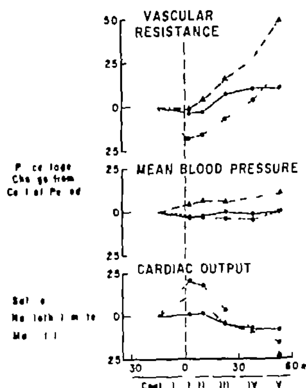


Fig 1 Sequential changes in systemic hemodynamics induced by injection of either saline, mannitol or sodium iothalamate. Five animals were used to obtain the data for saline (solid dot) while 7 animals were included in the sodium iothalamate results (solid triangles) and 8 in the mannitol (open circles) The five postinjection clearance intervals (I to V) are demarcated along the abscissa immediately below the time axis.

when k is the Donnan factor [16] The per cent of filtered sodium or chloride reabsorbed was derived as follows

$$\%T = \frac{F - U\,V}{F} \times 100$$

when F represents the filtered load of the electrolyte being measured Nonchloride nonurea solute was the difference between the total solute excretion ($U_O\,V$) and the sum of the principle urinary electrolyte excretion ($U_N V$ $U_K V$ $U_{Cl} V$) and urinary urea (U V)

Results

Systemic hemodynamic response to left ventricular injection-early effects Equiosmolar amounts of mannitol and sodium iothalamate resulted in an increase of cardiac output of 21 and 25 per cent respectively 15 sec after injection while systemic resistance fell by 23 and 29 per cent. Comparable volume of isotonic saline had no significant effect on these hemodynamic variables. These results are similar to those reported previously from this laboratory in awake men and anesthetized dogs,[1-4] in which we concluded that this hemodynamic effect was primarily due to the hypertonicity of the injectate

Prolonged hemodynamic effects of left ventricular injection Fig 1 depicts the percentage change from the control period of the cardiac output for all three materials injected The mean values recorded for each animal group during the control period are shown in Table I Cardiac output was significantly increased ($p < 0.05$) at the 5 minute interval (Period I Fig 1) in animals given mannitol and was significantly lower ($p < 0.05$) after one hour

Table I Comparative hemodynamic parameters during the control interval for different animal groups

Parameter (No. of animals)	Saline (5)	Na iothalamate (7)	Mannitol (8)
Cardiac output (ml./min./kg.)	152 ± 15	166 ± 21	183 ± 15
Mean blood pressure (mm. Hg)	126 ± 3	130 ± 4	131 ± 3
Systemic vascular resistance (mm Hg/L./min.)	50 ± 4	46 ± 4	48 ± 5

(Period V Fig 1) in animals receiving iothalamate. The decreased cardiac output at Period V in the animals given mannitol was not significant ($p > 0.1$) The late fall in cardiac output induced by the injection of sodium iothalamate was reversed in the two animals in which urine volume was replaced (Fig 2) The fall in cardiac output recorded in Period V (Fig 1) in the animals receiving sodium iothalamate was associated with a significant rise ($p < 0.05$) in both systemic vascular resistance and mean systemic blood pressure. The injection of mannitol caused a significantly decreased vascular resistance during Periods I to III while the increase noted at one hour (Period V) was also significant. Significance was determined by the "t" test for paired observations.[11]

Changes in urine volume and solute excretion following left ventricular injection of one of the three solutions Fig 3 is a plot of the sequential change in the mean rate of urine excretion expressed per kilogram body weight, following injection of each of the three agents. The abrupt, sustained diuresis induced both by sodium iothalamate and mannitol represent a significant increase over the control interval. The integrated mean difference in urine flow between the control and postinjection period was +0 2 ml per hour per kilogram for saline, +5.5 mL per hour per kilogram for sodium iothalamate and +2 9 mL per hour per kilogram for mannitol. Mean values for solute excretion before and after left ventricular injection were saline 2,800 ± 159 µOsm per hour per kilogram preinjection compared to 2,815 ± 374 µOsm per hour per kilogram postinjection sodium iothalamate 2 403 ± 67 µOsm per hour per kilogram preinjection versus 5 000 ± 280 µOsm per hour per kilogram postinjection and mannitol 2 47? ± 65 µOsm per hour per kilogram preinjection versus 3,541 ± 309 postinjection

Although the change in the rate of solute excretion following the injection of sodium iothalamate parallels the increase in urine flow rate the same is not true for the late postinjection observations in the animals given mannitol Because of this divergence the urinary excretion of sodium chloride nonchloride anion and nonurea nonelectrolyte solute for each of the three animal groups were tabulated and the per cent changes from the control period are plotted in Figs 4 and 5 The mean ± S D control values for these parameters are shown in Table II As expected the injection of sodium iothalamate was associated with a substantial increase in nonchloride anion excretion (Fig 4) since iothalamate once filtered is excreted without further modification by tubular action[11] Furthermore the iodine of sodium iothalamate does not dissociate and therefore does not interfere with the titration of chloride ion in the urine (Porter G A. and Kimsey J., unpublished observations) Similarly mannitol a completely filterable nonreabsorbable uncharged molecule results in a sustained increase in the nonurea, nonelectrolyte solute excretion (Fig 4) The marked

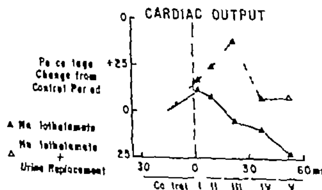


Fig. 2 Comparison of the sodium iothalamate-induced changes in cardiac output with and without replacing urine volume. Format identical to Fig. 1.

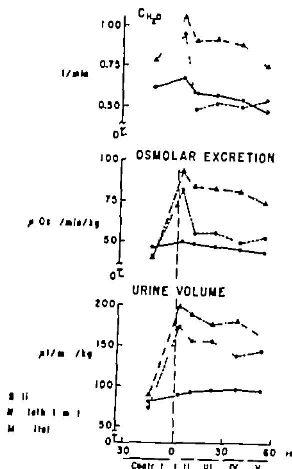


Fig 3 Sequential changes in urine volume osmolar excretion, and free water clearance (C_{H_2O}) following injection (time 0) of either saline, mannitol, or sodium iothalamate. Data from the same animals included in Fig 1 were used to construct this figure. The five postinjection clearance intervals (I to V) are demarcated along the abscissa immediately below the time axis.

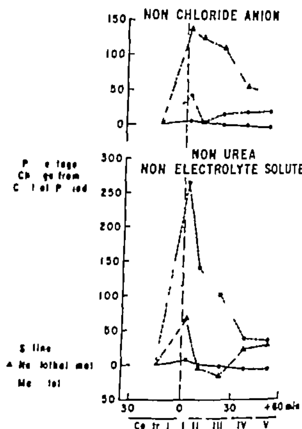


Fig 4 Sequential change in urinary solute excretion following injection of either saline mannitol, or sodium iothalamate. The format is similar to Fig. 3 except that the induced changes are expressed as a percentage change from the control values recorded during the preinjection interval.

increase in urinary sodium excretion following sodium iothalamate was expected because of the significant sodium load associated with iothalamate injection (Fig 5) However the significant increase in urinary chloride ($p < 0.05$) excretion following iothalamate (Fig 5) was unexpected

To evaluate the significance of the increased chloruresis associated with iothalamate injection the mean percentages of filtered sodium and filtered chloride reabsorbed by the renal tubules for each of the three animal groups were calculated and are summarized in Fig 6 Sodium iothalamate was the only injectate which caused a significant decrease in both tubular sodium and chloride reabsorption when compared to the preinjection values The decrease in tubular chloride reabsorption indicates that the presence of the negatively charged nonreabsorbable iothalamate ion in the glomerular filtrate does not completely account for the increased sodium diuresis which regularly follows the left ventricular injection of sodium iothalamate. In other words, if the reduced tubular reabsorption of sodium were due simply to the iothalamate ion then tubular chloride reabsorption should not be altered from the preinjection values.

To obtain more precise information concerning the significance of any difference in the pattern of urinary solute excretion caused by the two hypertonic agents iothalamate-^{131}I was injected and its urinary excretion measured in two animals. For comparison the urinary content of mannitol was specifically measured in two additional animals following left ventricular injection The mean excretion rates for

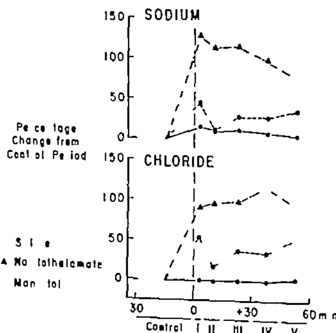


Fig. 5 Sequential change in urinary sodium and chloride excretion following injection of either saline, mannitol or sodium iothalamate. The format is identical to Fig. 4

Table II *Comparative solute excretion during control interval for different animal groups*

Parameter (*N* of animals)	*Saline* (5)	*N* *Iothalamate* (7)	*Mannitol* (8)
$U_{Na}V$ (μEq/min.)	207 ± 39	285 ± 90	228 ± 73
$U_{Cl}V$ (μEq/min.)	170 ± 36	213 ± 84	160 ± 68
U_AV^* (μEq/min.)	110 ± 11	143 ± 15	111 ± 13
$U_{solute}V\dagger$ (μM/min.)	176 ± 47	149 ± 53	178 ± 39

$^*U_AV$ $U_{Na}V + U_KV$ $U_{Cl}V$
$\dagger U_{solute}V$ $U_{osm}V$ $U_{Na}V + U_KV + U_{Cl}V + U_AV + U_{urea}V$

sodium iothalamate or mannitol and chloride in the latter studies are shown in Fig 7 The pattern and magnitude of urinary excretion of sodium iothalamate parallels that of mannitol however the sustained increase in urinary chloride excretion associated with the injection of sodium iothalamate is missing with mannitol.

In an additional animal the effect of nephrectomy on the plasma disappearance curve of iothalamate ^{125}I was measured and compared to the mean disappearance curves in the two dogs with intact kidneys. The nearly flat slope of the plasma radioactivity decay obtained from the nephrectomized dog, plus the low calculated excretion rate (Table III) confirm that sodium iothalamate elimination is principally dependent upon functionally intact kidneys. Using the formulation of Landes and associates [11] the volume of distribution and excretion rate for iothalamate ^{125}I and mannitol were calculated and compared with inulin. These data are summarized in Table III The minor difference between inulin and the other two compounds is probably the result of the technique used in administering the agents since inulin was given by constant infusion while the other two were administered as a single bolus. However these

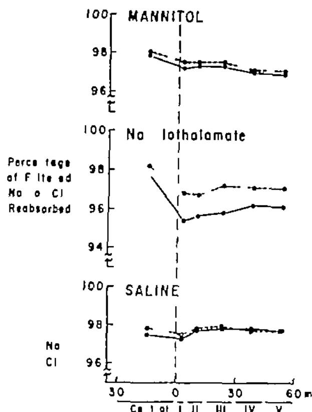


Fig 6 Sequential change in percentage of filtered sodium and chloride undergoing tubular reabsorption following injection of either saline mannitol or sodium iothalamate. The solid dots represent filtered sodium reabsorption while the open circles depict chloride.

results do confirm that iothalamate distribution is limited to the extracellular compartment.

Changes in renal function following left ventricular injection Fig 8 is a sequential plot of the mean percentage changes in glomerular filtration rate (inulin clearance) renal plasma flow (PAH clearance) renal vascular resistance and filtration fraction following injection in each of the three groups. During the initial 5 minute interval following injection of either sodium iothalamate or mannitol inulin clearances were significantly increased ($p < 0.05$) over the control period Otherwise inulin clearance was not significantly altered by the experimental manipulations.

With respect to renal plasma flow and vascular resistance only the mannitol induced changes proved to be statistically significant however this was true for all five experimental periods. Insight into the intrarenal vascular adjustments following injection of the three different agents can be gained from analysis of the changes in renal plasma flow compared to simultaneous changes in filtration rate the filtration fraction In animals given either isotonic saline or sodium iothalamate the

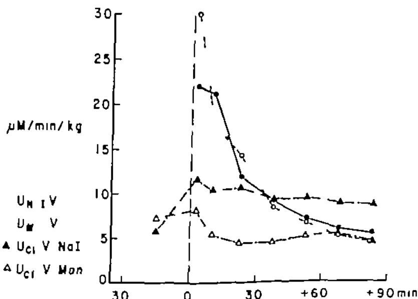


Fig 7 Serial urinary excretion of either mannitol or sodium iothalamate compared to simultaneous urinary chloride excretion in the same animals. The mannitol results (open circles and open triangles) are the mean of three animal experiments, while the sodium iothalamate results (solid dots and solid triangles) were derived from two animal experiments. Zero time represents the point of ventricular injection.

renal plasma flow fell while glomerular filtration rate remained unchanged thus the calculated filtration fraction rose (Fig 8) Only during the final postinjection clearance, Period V did filtration fraction significantly increase following sodium iothalamate, which corresponds to the point of maximum reduction in inulin space as shown in Table IV Conversely in animals given mannitol, although glomerular filtration rate was again unaffected renal plasma flow increased and the derived filtration fraction was significantly reduced as compared to the preinjection value. This change could result from alterations in pre and postglomerular capillary sphincter dynamics, causing filtration pressure (as reflected by inulin clearance) to remain unchanged while diminishing renal vascular resistance. This would account for a greater rate of renal plasma flow

Further evidence that the changes in renal function noted during the final clearance period following sodium iothalamate were in part the result of volume depletion is shown in Fig 9 In the two animals whose urine volumes were replaced during the first postinjection hour the late decline of PAH clearance and rise of renal vascular resistance were reversed. However the volume depletion did not explain the sodium iothalamate-induced alteration of tubular reabsorption of sodium and chloride since both parameters were significantly depressed over the control values despite replacement with artificial urine.

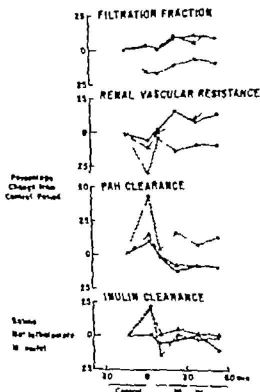


Fig. 8 Sequential changes in renal function induced by injection of either saline mannitol, or sodium iothalamate. Data from the same animals included in Figs. 1 and 3 to 6 were used to construct this figure. The format is identical to Fig 1

Table III *Distribution volume and excretion rate*

Experiment *	Distribution volume (% body wt.)		Excretion rate (ml./min./Kg.)	
	Iothalamate	*Inulin*	*Iothalamate*	*Inul*
D[illegible]	26 9	25 1	4 7	4 1
D[illegible]	19 6	18 1	4 3	4 4
D[illegible] (*)	20 3	20 1	0 7	—
D[illegible]	20 0†	17 3	3 1†	4 4
D[illegible]	17 1†	16 9	3 2†	4 2
D[illegible]	16 6†	16 3	3 7†	4 3

*X = Kaplanectomy
†Mannitol.

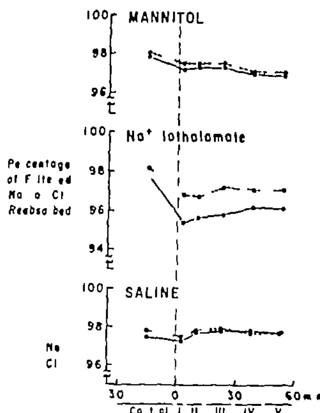


Fig 6 Sequential change in percentage of filtered sodium and chloride undergoing tubular reabsorption following injection of either saline mannitol or sodium iothalamate The solid dots represent filtered sodium reabsorption while the open circles depict chloride.

results do confirm that iothalamate distribution is limited to the extracellular compartment.

Changes in renal function following left ventricular injection Fig 8 is a sequential plot of the mean percentage changes in glomerular filtration rate (inulin clearance) renal plasma flow (PAH clearance) renal vascular resistance and filtration fraction following injection in each of the three groups During the initial 5 minute interval following injection of either sodium iothalamate or mannitol inulin clearances were significantly increased ($p < 0.05$) over the control period Otherwise inulin clearance was not significantly altered by the experimental manipulations.

With respect to renal plasma flow and vascular resistance only the mannitol induced changes proved to be statistically significant however this was true for all five experimental periods Insight into the intrarenal vascular adjustments following injection of the three different agents can be gained from analysis of the changes in renal plasma flow compared to simultaneous changes in filtration rate, the filtration fraction In animals given either isotonic saline or sodium iothalamate, the

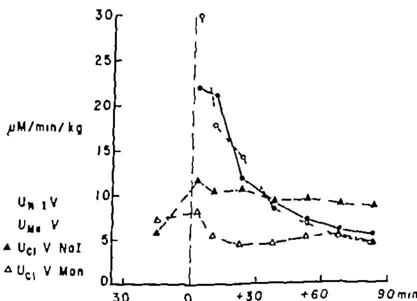


Fig 7 Serial urinary excretion of either mannitol or sodium iothalamate compared to simultaneous urinary chloride excretion in the same animals. The mannitol results (open circles and open triangles) are the mean of three animal experiments, while the sodium iothalamate results (solid dots and solid triangles) were derived from two animal experiments. Zero time represent the point of ventricular injection

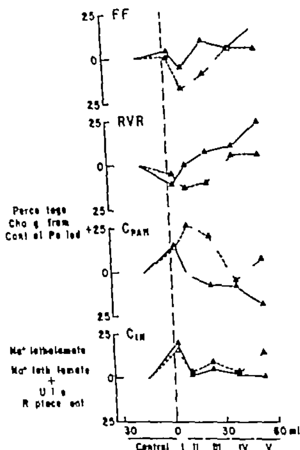


Fig. 9. Comparison of the sodium iothalamate-induced changes in renal function with and without urine volume replacement. Once again the format is identical to Fig. 2. The seven iothalamate animals who did not receive urine volume replacement are shown as solid triangles, while the results in the 2 animals given urine replacement during the iothalamate-induced diuresis are shown as open triangles.

filtered sodium reabsorbed from the proximal tubule.[14] The precise mechanism responsible for the decreased proximal tubular sodium reabsorption is unclear but significant expansion of the extracellular space is a prime condition for eliciting this response in the dog.[17] Because of the small volume of the injectate used in the present experiments plus a measured reduction in the inulin space following iothalamate induced diuresis (Table IV) expansion of the extracellular fluid space does not explain the reduced tubular reabsorption of sodium associated with the injection of sodium iothalamate. Also, it would seem unlikely that the transient rise in glomerular filtration rate which followed iothalamate injection accounts for the depressed tubular reabsorption of sodium since a similar change in filtration rate was noted with mannitol injection. This conclusion is supported by the observation of Lindheimer and co-workers,[17] who were unable to measure an augmented sodium excretion by increasing the glomerular filtration rate unless they simultaneously expanded the extracellular volume.

When tubular reabsorption is measured in the intact kidney proximal and distal tubular absorption cannot be separated as is the case with the micropuncture technique. However it has been suggested that changes in the rate of free water formation (C_{H_2O}) can be used as an index of the rate of distal tubular sodium reabsorption provided adequate prehydration of the animal is assured.[18] Since our animals were not undergoing water diuresis at the time

Table IV Change in inulin space (% body wt) following injection of three compounds

Experimental condition	*No*	*Control interval*	*V period*	*d* (%)*	*p†*
Saline	5	17 3 ± 1 0	18 2 ± 1 7	+5 2	-
Iothalamate	5	18 9 ± 1 8	14 0 ± 2 8	−25 9	+
Mannitol	5	18 7 ± 1 1	17 4 ± 2 5	−6 9	-
Angio and replace	2	18 4	18 9	+2 7	-

d = Mean difference bet een control interval and fifth postinjection interval.
†p + signifies probability < 0.05 while signifies probability > 0.05.

Discussion

In a previous study in which the im mediate hemodynamic effects of the rapid intravenous injection of three different radiopaque materials was compared with an equiosmolar amount of mannitol we concluded that osmolarity was a major determinant of the hemodynamic effects of angiocardiography [3] This same conclusion has been reported by other investigators using a wide variety of hypertonic solu tions.[14 17] However except for Frohlich [18] who investigated the hemodynamic conse quences of prolonged infusions of hyperos motic solution little is known regarding the possible hazards of the angiocardio-graphically induced diuresis. Furthermore only a limited number of investigations regarding the effect of the newer radiopaque materials on renal function have ap peared [19 20]

The late hemodynamic effects which fol low the injection of iothalamate seem more likely the result of volume depletion than due to a change in endothelial permeability as reported by Harrington and Wiedeman [21] The reversal of the hemodynamic deteriora tion by replacing urine volume (Fig 2) favors such conclusion Also the observa tions of Frohlich [18] who found a persistent reduction of systemic vascular resistance with prolonged infusions of hyperosmotic solutions tend to substantiate our inter pretation Although correction of the excess salt and water retention which characterize congestive heart failure is a primary thera peutic goal sudden changes in plasma vol ume may lead to unwanted hemodynamic responses.[22] A decrease in plasma volume as early as one-half hour after injection of contrast media has been reported by Iseri and associates.[22]

From the results obtained in this study the rapid injection of sodium iothalamate into the left ventricle is regularly followed by significant diuresis. However as was noted from comparing the pattern of solute excretion resulting from iothalamate with that induced by equiosmolar doses of man-nitol differences between renal effects of these two materials are evident. Like man nitol once iothalamate is filtered it is excreted without further modification by tubular activity [23,24] However under the experimental conditions we employed the renal response to iothalamate differed from mannitol since iothalamate induced a sig nificant decrease in the per cent of sodium and chloride reabsorbed from the tubule (Fig 6) but did not cause a decrease in renal vascular resistance.

Examination of Fig 7 suggests that the enhanced chloruresis which follows iothala mate injection is relatively independent of the excretion of iothalamate. One possi ble explanation for the disproportionately greater saline excretion in the iothalamate animals could be that the sodium iothala mate causes a hypernatremia Recently Kamm and Levinsky[25] have demonstrated that increasing the plasma sodium concen tration an average of 40 mEq per liter specifically inhibited tubular sodium reab-sorption by a direct intrarenal action in dogs. In our animals no significant change in plasma sodium occurred during the five postinjection clearance intervals. Another possible consideration would involve ex pansion of the extracellular fluid space which is known to diminish the per cent of

Summary

The prolonged effects of angiographic contrast media on systemic hemodynamics renal function, and solute excretion were compared to saline and mannitol in dogs lightly anesthetized with pentobarbital. Measurements of hemodynamic and renal function were made at intervals from one half hour before to one hour after rapid left ventricular injection. The progressive decline in cardiac output and renal plasma flow following iothalamate reflected diuresis induced volume depletion since these effects were reversed by replacing urine volume. This latter maneuver did not modify the iothalamate effect on renal solute excretion.

Although the rate and pattern of urinary excretion of iothalamate-¹²⁵I paralleled mannitol, the magnitude of the iothalamate diuresis significantly exceeded that induced by mannitol. The augmented iothalamate diuresis resulted from an increased urinary content of sodium chloride as confirmed by a significant decrease in tubular chloride reabsorption. Mannitol caused an increased renal plasma flow and a reduced renal vascular resistance while iothalamate effects were opposite. The effect of iothalamate on renal electrolyte reabsorption may represent a direct effect on renal tubular sodium transport.

The authors wish to thank Dr. Esmond Braun for assistance in the surgical preparation and Miss Jean Kimsey for her invaluable technical assistance.

REFERENCES

1. Kloster, F. E., Bristow, J. D., Jacobs, W. R., Porter, G. A., and Griswold, H. E.: Hemodynamic effects of angiocardiography, Invest. Radiol. 1:398, 1966.
2. Bristow, J. D., Porter, G. A., Kloster, F. E., and Griswold, H. E.: Hemodynamic changes attending angiocardiography, Radiology 88:939, 1967.
3. Kloster, F. E., Bristow, J. D., Porter, G. A., Judkins, M. P., and Griswold, H. E.: Comparative hemodynamic effects of equiosmolar injections of angiographic contrast materials, Invest. Radiol. 2:331, 1967.
4. Chien, S., Dellenback, R. J., Usami, S., and Gregersen, M. I.: Plasma trapping in hematocrit determination, Proc. Soc. Exp. Biol. Med. 119:1155, 1965.
5. Roe, J. H., Epstein, J. H., and Goldstein, N. P.: A photometric method for the determination of inulin in plasma and urine, J. Biol. Chem. 178:839, 1949.
6. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B., and Graber, M.: Renal clearance of substitute hippuric acid derivations and other aromatic acids in dog and man, J. Clin. Invest. 24:388, 1945.
7. Corcoran, A. C., and Page, I. H.: Determination of Mannitol in plasma and urine, J. Biol. Chem. 170:165, 1947.
8. Smith, H. W.: The kidney. Structure and function in health and disease, New York, 1951, Oxford University Press, p. 435.
9. Marshall, H. W., Helmholz, H. F., Jr., and Wood, E. H.: Physiologic consequences of congenital heart disease. In Hamilton, W. F., and Dow, P., editors: Handbook of physiology, Section 2, Circulation, Vol. 1, Washington, D. C., 1962, American Physiological Society, p. 428.
10. Levinsky, N. G., and Lalone, R. C.: The mechanism of sodium diuresis after saline infusion in the dog, J. Clin. Invest. 42:1261, 1963.
11. Snedecor, G. W.: Statistical methods, Ames, Iowa, 1962, Iowa State Univ. Press, p. 91.
12. Sigman, E. M., Elwood, C., Reagan, M. E., Morris, A. M., and Catanzaro, A.: The renal clearance of I¹²⁵ labelled sodium iothalamate in man, Invest. Urol. 2:432, 1965.
13. Landes, D., Szabo, A. J., Conn, R. B., J., Millam, D. F., and Green, G. G.: Compartment analysis of Hippuran-I¹³¹ distribution in intact and nephrectomized dogs, Amer. J. Physiol. 211:243, 1966.
14. Muirhead, E. E., Lackey, R. W., Bunde, C. A., and Hill, J. M.: Transient hypotension following rapid intravenous injections of hypertonic solutions, Amer. J. Physiol. 151:516, 1947.
15. Walcott, W. W., and Deyrup, I. J.: Mechanism of hypotension following intravenous injections of strongly hypertonic solutions, Amer. J. Physiol. 160:15, 1950.
16. Gordon, A. J., Brahms, S. A., Megibow, S., and Sussman, M. L.: An experimental study of the cardiovascular effects of Diodrast, Amer. J. Roentgen. 64:819, 1950.
17. Friesinger, G. C., Shaffer, J., Criley, J. U., Gaertner, R. A., and Ross, R. S.: Hemodynamic consequences of the injection of radiopaque material, Circulation 31:730, 1965.
18. Frohlich, E. D.: Prolonged local and systemic hemodynamic effects of hyperosmotic solutions, Arch. Int. Pharmacodyn. 161:154, 1966.
19. Davidson, A. J., Abrams, H. L., and Stamey, T. A.: Renal extraction of PAH in man following abdominal aortography, Radiology 85:1043, 1965.
20. Bower, J. D., Magee, J. H., and Lester, R. G.: The effect of renal angiography on the normal kidney, Surgery 60:545, 1966.
21. Harrington, G. J., and Wiedeman, M. D.: The effect of contrast media on endothelial permeability, Radiology 81:1108, 1963.
22. Murray, R. H., Thompson, L. J., Bowers, J. A., Steinmetz, E. F., and Albright, C. D.: Hemodynamic effects of hypovolemia in normal subjects and patients with congestive heart failure, Circulation 39:55, 1969.
23. Iseri, L. T., Kaplan, M. A., Evans, M. J., and Nickel, E. D.: Effect of concentrated contrast

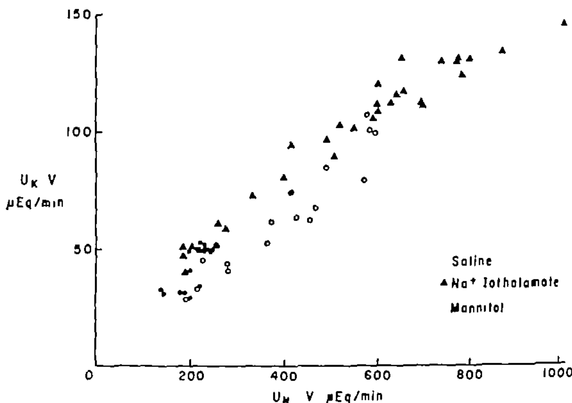


Fig *10* Plot of simultaneous urinary sodium and urinary potassium excretion rates, in µEq per minute for saline (solid dots) mannitol (open circles) and sodium iothalamate (solid triangles)

study no significance can be ascribed to changes in C_{H_2O} with respect to tubular sodium transport However an alternate technique for indirect assessment of the functional integrity of the distal tubular sodium/potassium exchange site is a correlation plot of simultaneous urinary sodium and potassium excretion (Fig 10) As can be seen the simultaneous rates distribute along a common response for all three agents. If iothalamate significantly inhibited the distal tubular exchange site then one would predict that at any given rate of sodium excretion potassium excretion would fall below the distribution found with mannitol and normal saline Therefore interference with distal tubular sodium reabsorption at least at the sodium/potassium exchange site, does not account for the increased saluresis of iothalamate Another explanation of our results is that iothalamate exerts a direct effect on renal tubular cells to interfere with active sodium reabsorption This latter speculation has indirect support from the persistence of the chloruresis despite a rapid diminishing urinary concentration of iothalamate as noted from Fig 7 Finally the possibility that the unique effect of iothalamate on chloride reabsorption simply reflects the induced osmotic diuresis seems remote since Rapoport and West[23] demonstrated a direct relationship between the permeability of the anion used to induce an osmotic diuresis and the attendant chloride loss. Thus, iothalamate s infinitely low tubular permeability would have a lower chloride loss than mannitol whose permeability is greater[22] We found just the reverse in our experiments

The absence of a decrease in renal vascular resistance in the animals given iothalamate as compared to the definite decrease following mannitol administration is somewhat surprising since Goldberg and Lilienfield[24] reported a fall in renal vascular resistance in the intact dog kidney following infusion of hyperosmotic solutions of mannitol dextran or sodium chloride This same observation has been extended to the isolated dog kidney[25] Thus it would appear that iothalamate does not produce the same effects on renal vascularity as does mannitol.

Summary

The prolonged effects of angiographic contrast media on systemic hemodynamics renal function and solute excretion were compared to saline and mannitol in dogs lightly anesthetized with pentobarbital Measurements of hemodynamic and renal function were made at intervals from one half hour before to one hour after rapid left ventricular injection. The progressive decline in cardiac output and renal plasma flow following iothalamate reflected diuresis induced volume depletion since these effects were reversed by replacing urine volume. This latter maneuver did not modify the iothalamate effect on renal solute excretion.

Although the rate and pattern of urinary excretion of iothalamate [125]I paralleled mannitol the magnitude of the iothalamate diuresis significantly exceeded that induced by mannitol. The augmented iothalamate diuresis resulted from an increased urinary content of sodium chloride as confirmed by a significant decrease in tubular chloride reabsorption. Mannitol caused an increased renal plasma flow and a reduced renal vascular resistance while iothalamate effects were opposite The effect of iothalamate on renal electrolyte reabsorption may represent a direct effect on renal-tubular sodium transport.

The authors wish to thank Dr Esmond Braun for assistance in the surgical prepar tion and Miss Jean Kinney for her invaluable technical assistance.

REFERENCES

1 Kloster F E Bristow J D Jacobs, W R Porter G A, and Griswold, H E Hemodynamic effects of angiocardiography Invest. Radiol. 1:398, 1966.
2 Bristow J D Porter G A, Kloster F E and Griswold H E. Hemodynamic changes trending angiocardiography Radiology 88:939 1967
3 Kloster F E Bristow J D Porter G A, Judkins, M P and Griswold H. E Comparative hemodynamic effects of equiosmolar injections of angiographic contrast materials, Invest. Radiol. 2:353 1967
4 Chien, S Dellenback, R. J Usami, S and Gregersen, M I Plasma trapping in hematocrit determination, Proc. Soc. Exp. Biol. Med. 119 1155 1965
5 Ros, J H Epstein, J H and Goldstein, N P A photometric method for the determination of inulin in plasma and urine J Biol. Chem. 178:839 1949
6 Smith, H. W Finkelstein, N Aliminosa, L., Crawford B and Graber M: Renal clearance of substitute hippuric acid derivations and other aromatic acids in dog and man, J Clin. Invest. 24:388, 1945.
7 Corcoran, A. C. nd Page I H.: Determination of Mannitol in plasma nd urine J Biol. Chem. 1 # 165 1947
8 Smith, H. W: The kidney Structure and function in health and disease, New York, 1951 Oxford University Press, p. 485.
9 Marshall H W Helmholz, H. F., J and Wood E. H. Physiologic consequences of congenital heart disease I Hamilton, W F and Dow P editors Handbook of physiology Section 2, Circulation, Vol. 1 Washington, D C., 1962, American Physiological Society p. 428.
10. Levinsky N G., and Lalone, R. C. The mechanism of sodium diuresis after saline infusion i the dog, J Clin. Invest. 42 1261 1963.
11 Snedecor G. W Statistical methods, Ames, Iowa, 1962, Iowa State Univ Press, p. 91
12 Sigman, E. M. Elwood, C Reagan M E., Morris A. M and Catanzaro, A.: The renal clearance of I[125] labelled sodium iothalamate I man, Invest. Urol. 2 432, 1965.
13. Landes, D Sabo, A J Conn, R. B J Milam, D F nd Green, G G. Compartment analysis of Hippuran-I[131] distribution in intact nd nephrectomized dogs, Amer J Physiol. 211:143 1966.
14. Muirhead, E. E., Lackey R. W Bunde C, A., and Hill J M Transient hypotension following rapid intra enous injections of hypertonic sol tions, Amer J Physiol. 151:516, 1947
15 Walcott, W W nd Deyrup, I J Mechanism of hypotension following intravenous injections of strongly hypertonic sol tions, Amer J Physiol. 160 13 1950
16 Gordon, A. J Brahms, S. A., Megibow S nd Sussman, M L. An experimental study of the cardiovascular effects of Diodrast, Amer J Roentgen. 64:819 1950.
17 Friesinger G C., Shaffer J Criley J U Gaertner R. A and Ross, R S. Hemodynamic consequences of the injection of radiopaque material Circulation 31 730 1965.
18. Frohlich, E. D Prolonged local and systemic hemodynamic effects of hyperosmotic solutions Arch. Int. Pharmacodyn. 161 154, 1966.
19 Davidson, A. J Abrams, H L., nd Stamey T A., Renal extraction of PAH in man following abdominal aortogr phy Radiology 85 1043, 1965.
20. Bower J D Magee, J H., and Lester R. G. The effect of renal angiography on the normal kidney Surgery 60:515, 1966.
21. Harrington, G. J and Wiedeman, M D. The effect of contrast media on endothelial permeability Radiology 84 1108, 1965
22. Murray R. H Thompson, L. J Bowers, J A., Steinmetz, E. F and Albright, C. D Hemodynamic effects of hypovolemia i normal s bjects and patients with congestive heart failure Circulation 39:55, 1969
23 Iserl, L. T Kaplan, M. A., Evans, M J and Nickel, E. D., Effect of concentrated contrast

media during angiography on plasma volume and plasma osmolality AMER. HEART J 69:154 1965
24 Griep R. J and Nelp, W B Mechanism of renal excretion of I[125] sodium iothalamate (Conray) J Nucl Med. 7:370 1966
25 Kamm D E. and Levinsky N G Inhibition of renal tubular sodium reabsorption by hypernatremia J Clin. Invest. 44:1144 1965
26 Brenner B M Bennett C. M and Berliner R W The relationship between glomerular filtration rate and sodium reabsorption by the proximal tubule of the rat nephron J Clin Invest. 4 :1358, 1968
27 Lindheimer M D Lalone R C. and Levinsky N G Evidence that an acute increase in glomerular filtration has little effect on sodium excretion in the dog unless extracellular volume is expanded J Clin. Invest. 46:256, 1967
28. Stein R. M Abramson R. G Kahn, T and Levitt M F Effect of hypotonic saline loading in hydrated dog evidence for a saline-induced limit on distal tubular sodium transport, J Clin. Invest, 46:1205 1967
29 Rapoport, S and West, C. D Ionic antagonism effect of various anions on chloride excretion during osmotic diuresis in the dog. Amer J Physiol 162:668, 1950.
30. Goldberg A. H., and Lilienfield L. S. Effects of hypertonic mannitol on renal vascular resistance Proc. Soc. Exp. Biol. Med. 119:635, 1965.
31 Harvey R. B Vascular resistance changes produced by hyperosmotic solutions, Amer J Physiol 199:31 1960.

New method to measure phasic coronary blood velocity in man

A. Benchimol, M.D.
H. Fred Stegall, M.D.
John L. Gartlan
Phoenix, Ariz.

Several techniques have been used in the past to study coronary flow in man. They include the nitrous oxide inhalation,[1-4] injection of radioactive substance,[7-11] and others.[12-14] Despite some limitations of the measurements made with these approaches, they have provided a means of better understanding of the coronary circulation in health and disease. However, none of them allow measurements of *phasic* instantaneous or continuous flow on beat-to-beat basis.

Franklin's[14] development of an ultrasonic Doppler flowmeter allowed measurement of phasic blood velocity in man using either the transcutaneous approach or probes surgically implanted around the blood vessels. Subsequently, Stegall and associates described a velocity probe in which the small piezoelectric crystals were mounted on a tip of a conventional cardiac catheter; as a result it became possible to measure phasic blood velocity from blood vessels or cardiac chambers not ordinarily accessible to transcutaneous examination.[15]

The purpose of the report is to describe our experience with the use of Doppler ultrasonic flowmeter catheter system to study *phasic coronary artery blood velocity* in man.

Material and methods

Forty-five patients were studied, 27 men and 18 women. Their ages ranged from 15 to 79 years with a mean of 46 years. 10 were diagnosed as normal and the remaining 35 had various types of heart disease. In the disease group, 16 had mitral valve disease, 11 coronary artery disease, 8 aortic valve disease, 3 congenital heart disease and 7 were classified as miscellaneous. Selective coronary arteriograms using the Sones[24] technique were obtained on 32 patients.

Normal subjects were asymptomatic or had atypical chest pain; their cardiovascular functions were normal as defined by right and left heart pressures determined during catheterization, indicator dilution measurement of cardiac output, and selective cineangiocardiography. These patients were studied in the cardiac catheterization laboratory because of the presence of systolic murmurs or chest pain previously diagnosed as representing organic heart disease but, after examination, were classified as having a functional murmur or chest

From The Institute for Cardiovascular Diseases, Good Samaritan Hospital, Phoenix, Ariz.
Received for publication April 22, 1970.
Reprint requests to: Dr. A. Benchimol, Good Samaritan Hospital, P.O. Box [illegible], 1033 East McDowell Rd., Phoenix, Ariz. [illegible].

media during angiography on plasma volume and plasma osmolality AMER HEART J 69:154 1965

24 Griep, R. J and Nelp W B Mechanism of renal excretion of I[131] sodium iothalamate (Conray) J Nucl Med 7:370 1966.

25 Kamm D E. and Levinsky N G Inhibition of renal tubular sodium reabsorption by hypernatremia J Clin Invest 44:1144 1965

26 Brenner B. M Bennett C. M., and Berliner R. W The relationship between glomerular filtration rate and sodium reabsorption by the proximal tubule of the rat nephron J Clin Invest. 47:1358 1968

27 Lindheimer M D Lalone R. C and Levinsky N G Evidence that an acute increase in glomerular filtration has little effect on sodium excretion in the dog unless extracellular volume is expanded, J Clin. Invest. 46:256, 1967

28 Stein R. M Abramson R. G Kahn, T and Levitt, M F Effect of hypotonic saline loading in hydrated dog: evidence for a saline-induced limit on distal tubular sodium transport, J Clin. Invest. 46:1205 1967

29 Rapoport, S. and West, C. D Ionic antagonism: effect of various anions on chloride excretion during osmotic diuresis in the dog Amer J Physiol 162:668 1950.

30. Goldberg A. H and Lilienfield, L. S. Effects of hypertonic mannitol on renal vascular resistance Proc Soc. Exp. Biol. Med 119:635, 1965.

31 Harvey R B Vascular resistance changes produced by hyperosmotic solutions, Amer J Physiol 199:31 1960.

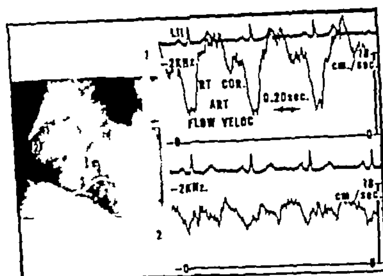


Fig. 4 Lead II of the electrocardiogram and right coronary artery blood velocity in a 31 year-old man with coronary artery disease. The tracing labeled *1* was taken with the tip of the sensing catheter near the ostia of the right coronary artery in position indicated on the coronary arteriogram. Tracing *2* was taken near the obstructive lesion in the proximal third segment of the right coronary artery. The coronary arteriogram illustrated in this figure was taken in left anterior oblique position. Note continuous velocity pattern in the tracing recorded near the obstruction. See text.

normal coronary arteries). In 4 of these 8 patients (2 with normal coronary arteries and 2 with coronary artery disease) this drug resulted in a significant increase in peak systolic and diastolic blood velocities. Increase varied from 10 to 40 per cent of the control values with the maximal rise in peak diastolic blood velocity occurring between 30 and 60 seconds after administration of this drug (Fig. 6) and the full effect lasting from 2 to 3 minutes. This maximal increase in blood velocity coincided with a maximal reduction in the arterial and right ventricular pressures, indicating that an appreciable reduction in coronary vascular resistance had occurred.

Discussion

This study demonstrates the feasibility of obtaining continuous measurement of instantaneous phasic coronary blood velocity in man via a catheter tip flowmeter. To our knowledge, this is the first time such measurements have been obtained in intact, conscious man. Although more experience is required to ascertain the definitive value of this technique in studying coronary circulation in man, it appears that at least in some patients, useful information can be derived from such measurements.

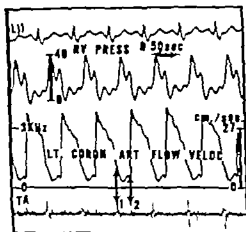


Fig. 5 Lead II of the electrocardiogram, right ventricular (*RV*) pressure, left coronary artery blood velocity and phonocardiogram at the tricuspid area (*TA*) in a 48-year-old man with mitral stenosis and normal coronary arteriograms. During the recording, the patient had sinus tachycardia with heart rate of 110 per minute. Note small systolic fraction on the coronary blood velocity curves.

A variety of techniques have been used in the past to study coronary flow in man and animals. These include nitrous oxide inhalation[1-4] and radioisotopic techniques using ^{42}K, ^{86}Rb, and ^{131}I[7-11]. These tech

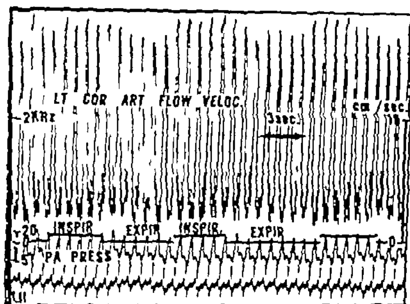


Fig 3 Left coronary artery blood velocity pulmonary artery pressure (P 1) and Lead II of the electrocardiogram in a 45-year-old woman with chest wall pain and normal coronary arteriogram. Note the variation on the peak diastolic blood velocity during normal phases of respiration.

diffuse obstruction of the right or left coronary arteries did not show any significant differences in the wave form pattern and the curves had essentially the same contour as described for normal subjects However in one patient with almost total occlusion of the proximal third segment of the right coronary artery marked abnormalities in the blood velocity pattern were observed as shown in Fig 4 when the velocity probe was placed at the ostia of the right coronary artery a large systolic wave was recorded at that level and its amplitude was as high as the peak diastolic wave The tracing however fell quite abruptly to the near baseline level at the end of atrial contraction to rise again with the next systolic cycle As the velocity probe was advanced down the artery to an area near the obstruction there appeared a marked change in the velocity curves The phasic pattern almost disappeared and the tracing assumed a *continuous velocity* pattern throughout both systole and diastole This variation from the normal wave form pattern could be reproduced repeatedly by advancing and withdrawing the catheter

Cardiac arrhythmias

SINUS TACHYCARDIA Sinus tachycardia in 3 patients indicated that heart rates above 110 per minute resulted in a decrease in the systolic fraction of the velocity curve the diastolic fraction decreased only slightly (Fig 5)

EXTRASYSTOLES Extrasystoles had a variable influence on peak diastolic flow velocity depending on the timing of the extrasystoles during the cardiac cycle (Fig 1) Premature contractions occurring very early in the cardiac cycle resulted in practically no measurable systolic blood velocity curves and the diastolic fraction was also decreased the shorter the interval between the extrasystolic beat and the preceding beat the smaller the peak velocity of systolic and diastolic velocities. These findings were independent of the site of origin of the extrasystolic beat, being seen during atrial nodal and ventricular extrasystoles. However post-extrasystolic augmentation of the diastolic fraction was somewhat greater after a ventricular extrasystole than seen after atrial or nodal extrasystole

ATRIAL FIBRILLATION In patients with atrial fibrillation the coronary blood velocity varied from beat to beat the peak velocity of the diastolic fraction for each beat however was not directly portional to the preceding cycle length (Fig 2)

Effect of nitroglycerin.

The effect of administration of sublingual nitroglycerin (1/150 grain) on coronary blood velocity was examined in 8 patients (3 with coronary arte

made in a patient with near total occlusion of the proximal segment of the right coronary artery which revealed that near the occlusion of the blood velocity pattern was continuous throughout the entire cardiac cycle due to a large increase in the systolic fraction. Indeed the pattern was strikingly similar to that seen in a peripheral vein. Although more observations are required to confirm this finding it appears that an increase in blood velocity during systole is an important compensatory mechanism in a patient with severe perfusion deficit due to coronary artery disease. During reactive hyperemia, one often observes that the usually pulsatile flow velocity pattern in a peripheral artery changes to become more continuous, and the differences between peak (systolic) and average velocity are much reduced; thus it seems reasonable that a patient with large vessel coronary disease in whom the vascular resistance below the obstruction should be minimal, should present the sort of continuous velocity pattern noted here. The contribution of the systolic fraction to total coronary flow has been previously recognized in animal preparations and under normal circumstances at rest is approximately 15 to 30 per cent of the diastolic fraction.[11] However following release of coronary artery occlusion and during stimulation of the cardiac sympathetic system in dogs, the amount of the systolic flow increases up to 300 per cent of the control values.[12]

Our observations during cardiac arrhythmias emphasize the importance of cycle length and diastolic filling time in determining coronary blood velocity. This is well illustrated in conditions such as atrial fibrillation, tachycardia, and extrasystoles.

The preliminary observations on the effect of nitroglycerin in the coronary blood velocity suggests that this drug may indeed increase coronary blood flow in both normal subjects and in patients with coronary artery disease. However coronary resistance depends both on vessel caliber and perivascular muscle forces, and its changes in apparent resistance could also be ascribed to changes in the contractile processes in the ventricular wall.

The limitations of the technique used are essentially the ones described previously in the study of aortic and right atrial blood velocities.[1, 4] The catheter tip device when in close contact with the walls of the aorta senses large, low frequency Doppler shift signals which easily obscure the smaller flow velocity signals. Position of the catheter tip against the wall of the aorta or coronary artery probably accounts for the fact that adequate velocity signals, suitable for analysis, could be obtained in only 70 per cent of the patients on whom this technique had been tried. Again qualitative assessment (by ear) of signal quality is essential. This technique is not volumetrically quantitative since the cross-sectional area of the coronary artery is not known unless angiography is combined with velocity measurement. In addition the flow meter used in this study does not distinguish between "forward" and "reverse" flow; consequently retrograde flow in the coronary arteries, if any, could not be adequately appreciated. Fortunately most flow in the coronary artery—as in the renal and carotid arteries, among others—is forward (i.e., toward the perfused tissue).

One major advantage of this method is that it allows measurement of phasic coronary blood velocity without the necessity of calibrating each catheter probe since they are calibrated by the Doppler shift equation instead. There is little doubt that the curves obtained with this approach do represent blood velocity in the coronary arteries. This is based on the observations that the maximal velocity occurs during diastole, with only a small systolic fraction, or the reverse of what is normally observed in the aortic blood velocity curves.[14] There is no major vessel in the body known to present a velocity wave form of the type described here, other than the coronary arteries, which alone supply a tissue whose vascular resistance fluctuates so markedly with each heart beat.

Although more experience is needed it appears that this approach should be valuable in the study of coronary arterial circulation in man in a variety of normal and pathologic conditions; its major advantage is the capability of determining continuous instantaneous phasic coronary artery blood velocity in conscious, unanesthetized man.

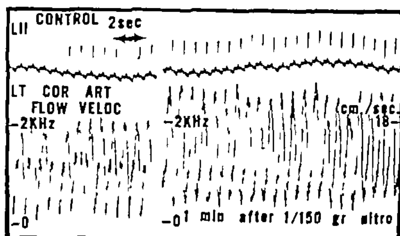


Fig 6 Lead II of the electrocardiogram and left coronary artery blood velocity in a 52 year-old male with coronary artery disease involving the left anterior descending and circumflex arteries The tracing of the right hand side was recorded one minute after sublingual administration of 1/150 grain of nitroglycerin. Note significant increase in peak coronary diastolic and systolic blood velocities after administration of this drug

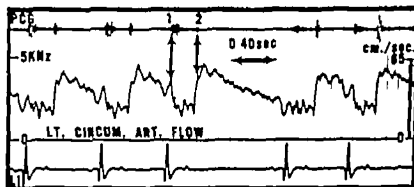


Fig 7 Dog No 24—Phonocardiogram left circumflex coronary artery flow velocity and Lead II of the electrocardiogram in a normal greyhound dog In this experiment, a probe was surgically implanted around the left circumflex artery four weeks prior to this measurement. This recording was used in a conscious, unanesthetized ambulatory animal Note that the wave form of coronary flow is essentially identical to the other figures. The first and second heart sound are properly indicated Sinus arrhythmia is present during the recording

niques measure mean flow rates and in addition are limited by the fact that these measurements cannot be made repeatedly for a period of time most important they do not measure *phasic flow* (i e instantaneous)

The velocity wave pattern described with this technique agrees with the observations of others made in chronically instrumented animals with either electromagnetic[21,28] or ultrasonic flowmeter[27] At the onset of isovolumic contraction there is abrupt decrease in coronary blood velocity as aortic pressure rises coronary blood velocity increases rapidly to a relatively low peak and decreases again during the period of slow ventricular ejection With the onset of isovolumic relaxation blood velocity rises rapidly peaking early in diastole at the time of rapid ventricular filling this peak is of a short duration and then the velocity tracing progressively returns toward baseline to reach its lowest point at the end of atrial systole The same velocity wave form pattern was seen in both right and left coronary arteries and was similar to post operative observations made in closed chest ambulatory conscious animals, with probes surgically implanted around the main branches of the coronary artery (Fig 7) In these preparations as seen here coronary blood flow is maximal during the early part of diastole with a much smaller fraction occurring during ventricular ejection (Fig 7)

Of particular interest was the observation

made in a patient with near total occlusion of the proximal segment of the right coronary artery which revealed that near the occlusion of the blood velocity pattern was continuous throughout the entire cardiac cycle due to a large increase in the systolic fraction. Indeed, the pattern was strikingly similar to that seen in a peripheral vein. Although more observations are required to confirm this finding it appears that an increase in blood velocity during systole is an important compensatory mechanism in a patient with severe perfusion deficit due to coronary artery disease. During reactive hyperemia, one often observes that the usually pulsatile flow velocity pattern in a peripheral artery changes to become more continuous and the differences between peak (systolic) and average velocity are much reduced thus it seems reasonable that a patient with large vessel coronary disease, in whom the vascular resistance below the obstruction should be minimal, should present the sort of continuous velocity pattern noted here. The contribution of the systolic fraction to total coronary flow has been previously recognized in animal preparations and under normal circumstances at rest is approximately 15 to 30 per cent of the diastolic fraction.[11] However following release of coronary artery occlusion and during stimulation of the cardiac sympathetic system in dogs, the amount of the systolic flow increases up to 300 per cent of the control values.[11]

Our observations during cardiac arrhythmias emphasize the importance of cycle length and diastolic filling time in determining coronary blood velocity. This is well illustrated in conditions such as atrial fibrillation tachycardia, and extrasystoles.

The preliminary observations on the effect of nitroglycerin in the coronary blood velocity suggests that this drug may indeed increase coronary blood flow in both normal subjects and in patients with coronary artery disease. However coronary resistance depends both on vessel caliber and perivascular muscle forces, and its changes in apparent resistance could also be ascribed to changes in the contractile processes in the ventricular wall.

The limitations of the technique used are essentially the ones described previously in the study of aortic and right atrial blood velocities.[8] The catheter tip device when in close contact with the walls of the aorta senses large low frequency Doppler shift signals which easily obscure the smaller flow velocity signals. Position of the catheter tip against the wall of the aorta or coronary artery probably accounts for the fact that adequate velocity signals, suitable for analysis, could be obtained in only 70 per cent of the patients on whom this technique had been tried. Again qualitative assessment (by ear) of signal quality is essential. This technique is not volumetrically quantitative since the cross-sectional area of the coronary artery is not known unless angiography is combined with velocity measurement. In addition the flow meter used in this study does not distinguish between "forward" and "reverse" flow consequently retrograde flow in the coronary arteries if any could not be adequately appreciated. Fortunately most flow in the coronary artery—as in the renal and carotid arteries among others—is forward (i.e. toward the perfused tissue).

One major advantage of this method is that it allows measurement of phasic coronary blood velocity without the necessity of calibrating each catheter probe, since they are calibrated by the Doppler shift equation instead. There is little doubt that the curves obtained with this approach do represent blood velocity in the coronary arteries. This is based on the observations that the maximal velocity occurs during diastole with only a small systolic fraction or the reverse of what is normally observed in the aortic blood velocity curves. There is no major vessel in the body known to present a velocity wave form of the type described here other than the coronary arteries, which alone supply a tissue whose vascular resistance fluctuates so markedly with each heart beat.

Although more experience is needed, it appears that this approach should be valuable in the study of coronary arterial circulation in man in a variety of normal and pathologic conditions its major advantage is the capability of determining continuous instantaneous phasic coronary artery blood velocity in conscious unanesthetized man.

Summary

Radio telemetry of phasic coronary artery blood velocity was described in 45 patients using a Doppler ultrasonic catheter flowmeter system The influence of major vessel disease respiration cardiac arrhythmias and nitroglycerin was examined The coronary blood velocity wave form was characterized by a major diastolic wave representing maximum acceleration of blood during ventricular diastole The systolic fraction of coronary blood velocity was normally less than 15 per cent of the diastolic component There was no appreciable difference between the right and left coronary artery blood velocity curves. In one patient with severe obstructive lesion of the right coronary artery the blood velocity profile was continuous throughout the cardiac cycle due to a marked increase in the systolic component The importance of cycle length in determining the magnitude of peak diastolic blood velocity was exemplified in patients with tachycardia and extrasystoles. Administration of nitroglycerin resulted in a 10 to 15 per cent increase in both systolic and diastolic fractions in 4/6 patients.

Although more experience with this technique is needed it appears that this approach is useful in determining instantaneous phasic coronary blood velocity from unexposed coronary arteries in conscious unanesthetized man

REFERENCES

1 Eckenhoff J E. Hafkensheil J H Harmel M H Goodale W T Lubin M Bing R. J and Kety S. S. Measurement of coronary blood flow by the nitrous oxide method Amer J Physiol. 152:356 1948
2. Gregg D E. Longino F H Green, P A. and Czerwonka, L. J A comparison of coronary flow determined by the nitrous oxide method and by a direct method using the rotameter Circulation 3:89 1951
3 Rowe, G. G The nitrous oxide method for determining coronary blood flow in man, AMER. HEART J 58:268 1959
4 Bing, R. J Hellems, H K. and Regan, T J Measurement of coronary blood flow in man Circulation 22:1 1960.
5. Brachfeld N Bozer J and Gorlin R. Action of nitroglycerin on the coronary circulation in normal and mild cardiac subjects, Circulation 19:697 1959
6. Gorlin, R. Brachfeld N., MacLeod C. and Bopp, P Effect of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work, Circulation 19:705 1959
7 Hansen A. T., Haxholdt, B F Husfeldt, E Lassen N A. Munck, O., Sorensen, H. Rabbek and Winkler K. Measurement of coronary blood flow and cardiac efficiency in hypothermia by use of radioactive krypton 85, Scand. J Clin. Lab. Invest. 8:182, 1956.
8 Levy M N., Imperial, E. S. and Zieski, H. Collateral blood flow to the myocardium as determined by the clearance of rubidium chloride Circ. Res. 9:1035 1961
9 Love W D and Burch, G. E. Differences in the rate of Rb uptake by several regions of the myocardium of control dogs and dogs receiving l-norepinephrine or pitressin, J Clin. Invest. 36:479 1957
10. Mena, I Kattus, A. A. Greenfield M A., and Bennett L. R. Effect of coronary blood flow on radioisotope dilution curves measured by precordial scintillation detection, Circ. Res. 9:911 1961
11 Notling D Mack, R., Luthy E. Kirsch M and Hogancamp C. Measurement of coronary blood flow and myocardial rubidium uptake with Rb J Clin. Invest. 37:921 1958.
12. Marchioro T Feldman, A., Owens, J C., and Swan H Measurement of myocardial blood flow Indicator-dilution technique, Circ. Res. 9:541 1961
13 Gorlin, R. and Storaasli, J P Transcoronary circulation time A new method of evaluating the coronary vascular system Circulation 11:943 1956.
14 Benchimol A., Maia I G and Maroko, P R. Selective coronary dye-dilution curves in normal subjects and in patient with coronary disease Amer J Cardiol. 22:844 1968.
15 Franklin D L. Schlegel W and Rushmer R F Blood flow measured by Doppler frequency shift of backscattered ultrasound, Science 134:564 1961
16. Franklin, D L. Schlegel W and Watson, N W Ultrasonic Doppler shift blood flowmeter Circuitry and practical application Proc. ISA Biomed. Science Instrument 1:309 1963
17 Stegall H F Stone H W Bishop V S., and Laenger C. A catheter tip pressure and velocity sensor Proc. 20th Ann. Conf Eng Med. Biol 27:4 1967
18. Benchimol A. Stegall, H. F Maroko, P R., Brener I and Gartlan J L. Aortic flow velocity in man during cardiac arrhythmias measured with the Doppler-catheter flowmeter system, AMER. HEART J 78:649 1969
19 Benchimol A. Stegall H. F Gartlan, J L. Barreto, E. C. Goldstein, M R., and Sandoval, J Right atrium and superior vena cava flow velocity in man measured with the Doppler catheter flowmeter telemetry system, Amer J Med. 48:303 1970.
20. Sones, F M J ., and Shirey E. K. Cine coronary arteriography Mod. Conc. Cardiovasc. Dis. 31:735 1962.
21 Granata L. Huvos, A. and Gregg D E.

Hemodynamic changes in coronary and mesenteric arterial beds following sympathetic nerve stimulation, Physiologist 4:42, 1961

22. Khouri, E. M., Gregg, D. E., and Lowensohn, H. S.: Flow in the major branches of the left coronary artery during experimental coronary insufficiency in the unanesthetized dog, Circ. Res. 23:99 1968.

23. Corday E., Gold, H., DeVera, L. B., Williams, J. H. and Fields, J. Effect of the cardiac arrhythmias on the coronary circulation, Ann. Intern. Med. 50:535 1959

24. Feinberg, H., Gerola, A., and Katz, L. N. Effect of hypoxia on cardiac oxygen consumption and coronary flow Amer J Physiol. 195:593, 1958.

25. Rayford, C. R., Havos, A., Khouri, E. M. and Gregg, D. E. Some determinant of coronary flow in intact dogs, Physiologist 4:92, 1961

26. Rodbard, S. Graham, G. R., and Williams, F Continuous and simultaneous measurement of total coronary flow venous retur nd cardiac output in the dog J Appl. Physiol. 6:311 1953

27. V Citters, R. L. nd Franklin, D L. Cardiovascular performance of Alaska sled dogs during exercise, Circ. Res. 24:33, 1969

Summary

Radio telemetry of phasic coronary artery blood velocity was described in 45 patients using a Doppler ultrasonic catheter flowmeter system The influence of major vessel disease respiration cardiac arrhythmias and nitroglycerin was examined The coronary blood velocity wave form was characterized by a major diastolic wave representing maximum acceleration of blood during ventricular diastole The systolic fraction of coronary blood velocity was normally less than 15 per cent of the diastolic component There was no appreciable difference between the right and left coronary artery blood velocity curves. In one patient with severe obstructive lesion of the right coronary artery the blood velocity profile was continuous throughout the cardiac cycle due to a marked increase in the systolic component The importance of cycle length in determining the magnitude of peak diastolic blood velocity was exemplified in patients with tachycardia and extrasystoles Administration of nitroglycerin resulted in a 10 to 15 per cent increase in both systolic and diastolic fractions in 4/6 patients.

Although more experience with this technique is needed it appears that this approach is useful in determining instantaneous phasic coronary blood velocity from unexposed coronary arteries in conscious unanesthetized man

REFERENCES

1 Eckenhoff J E Hafkenshell J H Harmel M H Goodale W T Lubin M Bing R J and Kety S S Measurement of coronary blood flow by the nitrous oxide method Amer J Physiol. 152:356, 1948.

2 Gregg D E Longino F H Green P A. and Czerwonka, L. J A comparison of coronary flow determined by the nitrous oxide method and by a direct method using the rotameter Circulation 3:89 1951

3 Rowe, G G The nitrous oxide method for determining coronary blood flow in man, AMER HEART J 58:268 1959

4 Bing, R. J Hellems, H K and Regan, T J Measurement of coronary blood flow in man Circulation 22 1 1960

5 Brachfeld N Bozer J and Gorlin, R.: Action of nitroglycerin on the coronary circulation in normal and mild cardiac subjects, Circulation 19:697 1959

6. Gorlin, R Brachfeld N., MacLeod, C. and Bopp, P: Effect of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work, Circulation 19:705 1959

7 Hansen, A. T., Haxholdt B. F Husfeldt, E., Lassen, N A. Munck, O Sorenson, H. Rahbek, and Winkler K.: Measurement of coronary blood flow and cardiac efficiency in hypothermia by use of radioactive krypton 85, Scand. J Clin. Lab. Invest. 8:182 1956.

8 Levy M N Imperial E S. and Zieski, H Collateral blood flow to the myocardium as determined by the clearance of rubidium chloride Circ. Res. 9:1035 1961

9 Love W D and Burch G E Differences in the rate of Rb uptake by several regions of the myocardium of control dogs and dogs receiving l-norepinephrine or pitressin, J Clin. Invest. 36:479 1957

10 Mena I Kattus, A. A., Greenfield M A., and Bennett L. R. Effect of coronary blood flow on radioisotope dilution curves measured by precordial scintillation detection Circ. Res. 9:911 1961

11 Notling D Mack R. Luthy E., Kirsch, M., and Hogancamp C. Measurement of coronary blood flow and myocardial rubidium uptake with Rb, J Clin. Invest. 37:921 1958.

12 Marchioro, T Feldman A., Owens, J C., and Swan H Measurement of myocardial blood flow Indicator-dilution technique, Circ. Res. 9:541 1961

13 Gorlin R and Stornaalli, J P: Transcoronary circulation time A new method of evaluating the coronary vascular system, Circulation 14:913 1956.

14 Benchimol A. Maia, I G and Maroko, P R.: Selective coronary dye-dilution curves in normal subjects and in patients with coronary disease, Amer J Cardiol 22:844 1968.

15. Franklin, D L. Schlegel W and Rushmer R. F: Blood flow measured by Doppler frequency shift of backscattered ultrasound Science 134:564 1961

16. Franklin D L. Schlegel W and Watson, N W Ultrasonic Doppler shift blood flowmeter Circuitry and practical application Proc. ISA Biomed Science Instrument 1:309 1963.

17 Stegall H F Stone H W Bishop, V S., and Laenger C.: A catheter tip pressure and velocity sensor Proc. 20th Ann. Conf Eng Med. Biol 27:4 1967

18. Benchimol A. Stegall H. F., Maroko, P R Brener L. and Gartlan, J L. Aortic flow velocity in man during cardiac arrhythmias measured with the Doppler-catheter flowmeter system AMER HEART J 78:649 1969

19 Benchimol A. Stegall H F Gartlan, J L., Barreto, E. C. Goldstein M K. and Sandoval, J Right atrium and superior vena cava flow velocity in man measured with the Doppler catheter flowmeter telemetry system, Amer J Med. 48:303 1970.

20. Sones, F M Jr and Shirey E. K.: Cine coronary arteriography Mod. Conc. Cardiovasc. Dis. 31:735 1962

21 Granata L. Huvos, A. and Gregg D E:

Hemodynamic changes in coronary and mesenteric arterial bed following sympathetic nerve stimulation, Physiologist 4:32, 1961
22. Khouri, E. M., Gregg, D. E., and Lowensohn, H. S. Flow in the major branches of the left coronary artery during experimental coronary insufficiency in the unanesthetized dog. Circ Res. 23:99, 1968.
23. Corday, E., Gold, H., DeVera, L. B., Williams, J. H., and Fields, J. Effect of the cardiac arrhythmias on the coronary circulation. Ann. Intern. Med. 50:535, 1959
24. Feinberg, H., Gerola, A., and Katz, L. N. Effect of hypoxia on cardiac oxygen consumption and coronary flow. Amer. J. Physiol. 195:593, 1958.
25. Rayford, C. R., Huvos, A., Khouri, E. M., and Gregg, D. E. Some determinants of coronary flow in intact dogs. Physiologist 4:92, 1961
26. Rodbard, S., Graham, G. R., and Williams, F. Continuous and simultaneous measurement of total coronary flow, venous return and cardiac output in the dog. J. Appl. Physiol. 6:311, 1953
27. Van Citters, R. L., and Franklin, D. L. Cardiovascular performance of Alaska sled dogs during exercise. Circ. Res. 24:33, 1969

Case reports

Entrance block: A previously unrecognized phenomenon associated with transthoracic demand pacemaker implantation

*Melvyn Rubenfire, M.D.**
*Gerald M. Breneman, M.D.***
*Rodman E. Taber, M.D.****
Detroit, Mich.

Since the introduction and clinical use of cardiac pacemakers in the late 1950's, much has been written regarding their use, indications, hazards, methods of function and malfunction, and means of detecting malfunction. We have recently observed what we believe to be a previously unreported type of malfunction of transthoracic demand pacemakers.

The chief complications of the early pacemakers, especially the General Electric model then using a stainless steel electrode, was exit block. This phenomenon was detected by the use of threshold analyzers and reported initially by Preston and associates.[1] The incidence of exit block from the General Electric pacemaker ranged up to 25 per cent and became a formidable problem.[2] Exit block from other pacemakers utilizing platinum iridium electrodes was less frequent.[3]

At the Henry Ford Hospital, we have implanted in excess of 250 pacemakers since 1961, of which over 50 have been of the demand type. The latter are now used almost exclusively in our institution. We have documented only one instance of exit block. Recently, we observed failure of suppression of the demand circuit in two cases of epicardial pacemaker implant. This was ultimately shown to be due to a disturbance of transmission at the electrode-myocardial junction and the pacemaker was functionally converted to a fixed-rate type resulting in competitive rhythm. The purpose of this report is to describe the phenomenon and suggest means of evaluating and treating cardiac pacemaker malfunction of this type.

Case reports

Patient 1. G. S. (136-50-88-0), a 46-year-old woman, presented on March 16, 1969, with a history of sudden blackout spells dating back to 1964 and occurring approximately five times in the week prior to admission. There was no significant past history. The physical examination, chest x-ray, electrocardiogram, and laboratory tests were all normal. On the evening of admission to the cardiac monitoring unit

From the Department of Medicine, Division of Cardiovascular Diseases, and the Department of Surgery, Division of Thoracic Surgery, Henry Ford Hospital, Detroit, Mich.
Received for publication Dec. 15, 1969.
Reprint requests to: Melvyn Rubenfire, M.D., Department of Cardiology, Sinai Hospital, 6767 W. Outer Dr., Detroit, Mich. 48235.
*Senior Fellow, Department of Medicine, Division of Cardiovascular Diseases.
**Associate Physician, Department of Medicine, Division of Cardiovascular Diseases.
***Associate Surgeon, Department of Surgery, Division of Thoracic Surgery.

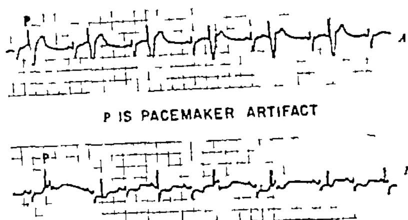


Fig. *1 A*. P tient I. Sinus rhythm nd artificial pacemaker competition is noted w th iatrogenic pacemaker-induced parasystole due to failure of suppression of the demand circuit. Pacemaker artifact is darkened for illustrati purposes *B*. P tient I. Persistent competiti rhythm between patient inus mechanism nd new demand pacemaker is seen. Myocard l refractory period are noted here the pacemaker artifact does not capture the ventricle.

the patient f lt faint and 12 second period of sinus arrest ithout ventricular or junctional escape beats as observed It as felt that the previous syncopal episodes ere related t similar phenomenon nd temporary transvenous pacemaker as placed in the right entricular pex on March 17 1969 On March 19 1969 transthoracic pacemaker of the demand type, Medtronic model, pulse generator N 5841 and Medtronic electrodes, model No. 5814 ere implanted Approximately five hours postopera tively she had the usually observed pericardial friction rub but also had developed signs of cardiac tamponade ith rising central enous pressure and hypotension The impression t that time as that cardiac tamponade secondary t hemopericardium had occurred in spite of the fact that rent had been made in the pericardium and left open prior to closure of the chest all The patient was returned to the operating room The myocardium was bulging through the pericardial rent and the pericardial opening as enlarged, although there as no tamponade. The patient as digitalized, since it as thought that the problem as an episode of acute dilatation resulting in phenomenon resembling constricting pericardium Following surgery all vital signs ere tabilized. Forty-eight hours postoper atively vital signs were normal. The lungs were ell expanded and the chest tube had been removed. On March 22, 1969 72 hours postoperatively the electrocardiogram (Fig. *1 A*) disclosed competition between the implanted pacemaker and the patient normal sinus rhythm, resulting in an iatrogenic pacemaker-induced ventricular parasystole. Because of the inappropriate firing of the pulse generator and lack of suppression by the patient sinus beats, it was felt that the blocking circuit of the demand pacemaker was not functioning properly The entire pulse generator was then replaced Postoperatively interference persisted as noted in Fig. *1 B* Competition persisted for the following three days in spite of therapy ith intravenous nd oral potassium. On March 27 1969 t 12 noon, the patient tarted on prednisone 15 mg four times daily 7½ hours after prednisone therapy was instituted, there w considerable suppression of the demand pacemaker nd only one inappropriate pacemaker potential could be seen on the monitor in 5-minute period. On March 28, 24 hours after prednisone w begun, there was no pacemaker competition. The lectrocardiogram howed diff se S-T and T abnormalities consistent ith pericarditis (Fig) nd the pericardial friction rub th t had been heard continuously as diminishing. The teroid dosage w tapered over the following 4 d ys, the pericardial friction rub disappeared, and the patient made good recovery There was no pacemaker competition and the demand unit noted t be functioning expected after carotid massage induced inus brady cardia. Myocardial biopsy obtained t the time of the first surgery showed normal myocardium.

Patient II P K (131-08-46) 65-year-old Caucasian man, admitted December 10, 1967 had had complet heart block diagnosed one year prior to admission nd pulse rate of 34 per minut had been documented. There as history of syncope and weakness. Past medical history as not contributory Physical examination showed him to be ell developed, with hoarse voice. Atelectatic râles ere heard in both lungs. The left border of cardiac d llness was in the midclavicular line in the fifth intercostal space There was varying intensity of the first heart sound. A Grade 2/6 systolic ejection murmur was audible t the base Brachial cuff blood pressure as 200/64 and the pulse was 48 per minute. The jugular enous pulse disclosed cannon ves. The abdomen, extremities, and results of neurologic examinations ere normal. The initial electrocardiogram (Fig 3 *A*) as interpreted as first degree trioventricular block and complete right bundle branch block suggesting bilateral bundle

Case reports

Entrance block: A previously unrecognized phenomenon associated with transthoracic demand pacemaker implantation

*Melvyn Rubenfire, M.D.**
*Gerald M. Breneman, M.D.***
*Rodman E. Taber, M.D.****
Detroit, Mich.

Since the introduction and clinical use of cardiac pacemakers in the late 1950's, much has been written regarding their use, indications, hazards, methods of function and malfunction, and means of detecting malfunction. We have recently observed what we believe to be a previously unreported type of malfunction of transthoracic demand pacemakers.

The chief complications of the early pacemakers, especially the General Electric model then using a stainless steel electrode, was exit block. This phenomenon was detected by the use of threshold analyzers and reported initially by Preston and associates.[1] The incidence of exit block from the General Electric pacemaker ranged up to 25 per cent and became a formidable problem.[2] Exit block from other pacemakers utilizing platinum iridium electrodes was less frequent.[3]

At the Henry Ford Hospital, we have implanted in excess of 250 pacemakers since 1961, of which over 50 have been of the demand type. The latter are now used almost exclusively in our institution. We have documented only one instance of exit block. Recently, we observed failure of suppression of the demand circuit in two cases of epicardial pacemaker implant. This was ultimately shown to be due to a disturbance of transmission at the electrode-myocardial junction and the pacemaker was *functionally converted to a fixed rate type* resulting in competitive rhythm. The purpose of this report is to describe the phenomenon and suggest means of evaluating and treating cardiac pacemaker malfunction of this type.

Case reports

Patient 1. G. S. (136-50-88-0), a 46-year-old woman, presented on March 16, 1969, with a history of sudden blackout spells dating back to 1964 and occurring approximately five times in the week prior to admission. There was no significant past history. The physical examination, chest x-ray, electrocardiogram, and laboratory tests were all normal. On the evening of admission to the cardiac monitoring unit,

From the Department of Medicine, Division of Cardiovascular Diseases, and the Department of Surgery, Division of Thoracic Surgery, Henry Ford Hospital, Detroit, Mich.
Received for publication Dec. 15, 1969.
Reprint requests to: Melvyn Rubenfire, M.D., Department of Cardiology, Sinai Hospital, 6767 W. Outer Dr., Detroit, Mich. 48235.
*Senior Fellow, Department of Medicine, Division of Cardiovascular Diseases.
**Associate Physician, Department of Medicine, Division of Cardiovascular Diseases.
***Associate Surgeon, Department of Surgery, Division of Thoracic Surgery.

January 1971 Vol 81 No. 1, pp. 10 10?

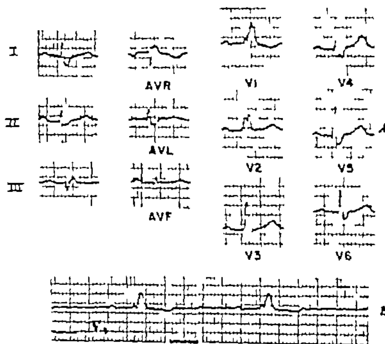


Fig. 3 4 Patient II. Preoperative electrocardiogram demonstrates complete right bundle branch block and first degree trioventricular block. The combination suggests bilateral bundle branch block. B I tient II Lead V on day of admission demonstrates right bundle branch block pattern nd high-grade trioventricular dissociation ppearing as 2 1 trioventricular block.

type of pacemaker will revert to a regular preset rate. Regardless of the type, demand pacemaker function is dependent on the suppression of the pacemaker or stimulation of the pacemaker by the myocardial impulse. If this impulse fails to reach the pulse generator an "entrance block to the pacing unit can be said to exist. This phenomenon, observed in the two cases described has been noted by others [4] with transvenous pacemakers and we indeed have seen this as well If one places the transvenous electrode in the pulmonary outflow tract the electrical impulse developed by the myocardium fails to reach the electrode and there is no suppression of the demand unit. It has also been demonstrated that accumulation of fibrin at the tip of transvenous electrodes or areas of myocardial fibrosis may result in a reduced millivoltage stimulus from the myocardium with resultant failure to suppress the pulse generator It is for this reason that Goetz and associates recommend a safety factor of 3 1 ratio between millivoltage from the endocardial electrode and the 2 mv required to stimulate or inhibit the pulse generator depending on the demand model used (synchronous or standby) Thus, a minimum 6 mv complex would be required from the myocardium to fulfill these criteria. This phenomenon has not been recognized previously with transthoracic pacemakers.

Exit block and failure to capture the ventricle associated with transthoracic pacemakers is felt to be due to fibrosis of the myocardial electrode site or increase in myocardial resistance possibly due to inter electrode electrolysis. Other possibilities used to explain exit block that would also be appropriate to explain entrance block would be edema at the electrode site abscess formation poor electrical contact because of surgical technique or blood about the electrodes.[1] Beneficial therapeutic responses to steroids in some instances of exit block suggest either edema or an inflammatory mechanism although it has been shown that steroids even in

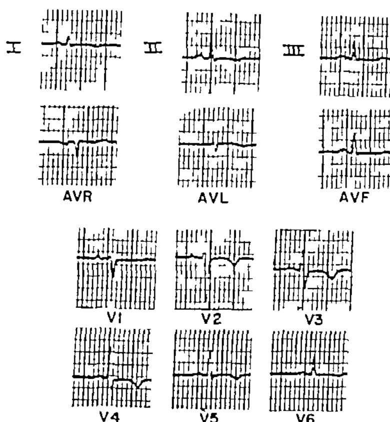


Fig 2 Patient 1 Forty-eight hours after steroid therapy was begun, electrocardiogram shows sinus rhythm without pacemaker artifacts and S-T and T abnormalities consistent with pericarditis.

branch block A subsequent rhythm strip (Fig 3 *B*) demonstrated a high-grade atrioventricular dissociation. The preoperative chest x-ray showed apical scarring and probable cavitary tuberculosis. After appropriate cultures the patient was begun on therapy for tuberculosis.

On Dec. 14 1967 after insertion of a temporary transvenous fixed-rate pacemaker a transthoracic demand pacemaker was inserted Medtronic model No. 5841 Medtronic electrodes No 5814 Postoperatively the patient did well except for mild cough and atelectasis. A pericardial friction rub was noted On Dec. 26, 1967 12 days postoperatively the electrocardiogram showed conversion from sinus rhythm to atrial flutter with a variable 3 1 and 4 1 block and the demand pacemaker was noted to be firing without an appropriate escape interval (Fig 4) This phenomenon was unrecognized at that time but proved to be of no consequence since it cleared spontaneously over the next 12 to 14 days. Interval electrocardiograms had not been obtained

Discussion

Pacing on demand has been utilized for the past several years particularly in cases of incomplete or transient heart block because of the competitive rhythms and risk of ventricular fibrillation noted at times with fixed rate pacing [4,8] Two types of noncompetitive pacemakers are in common usage. The ventricular synchronous pacemaker is synchronized to the R wave of the patient's own QRS complex and no delay occurs between the sensing of the QRS complex and emission of the stimulating impulse If the patient's QRS interval (ventricular contraction rate) is above a preset number of milliseconds the pacemaker will spontaneously revert to an automatic rate. When the myocardial contact electrode receives a stimulus, synchronization will restart. There is a refractory period of 200 msec following each pacemaker emission Therefore an early spontaneous ventricular contraction falling within 400 msec of the pacemaker impulse will not inhibit the next pacemaker beat. The second type or stimulus-blocking demand pacemaker is dependent on the myocardial impulse to inhibit the pacemaker beat with an escape interval of a preset number of milliseconds and refractory period of 150 to 250 msec. depending on the manufacturer A QRS complex of interventricular field between 2 and 35 mv (amplifier band width 4 to 200 cycles) is required to inhibit the pacemaker If no inhibition occurs, this

Failure of suppression of the pulse generator by the myocardial action potential is termed "entrance block." Mechanisms and therapeutic implications are discussed.

REFERENCES

1. Preston, T. A., Judge, R. D., Bowers, D. L., and Morris, J. D.: Measurement of pacemaker performance, Amer. Heart J. 1:92, 1966.
2. Bigelow, J. C., Herr, R. H., Wood, J. A., and Starr, A.: Clinical experience with Medtronic and General Electric transthoracic pacemakers, J. Thorac. Cardiovasc. Surg. 56:189, 1968.
3. Gerst, P. H., Bowman, F. D., Fleming, W. H., and Malm, J. R.: An evaluation of function and failure of artificial cardiac pacemakers, J. Thorac. Cardiovasc. Surg. 81:102, 1967.
4. Dreifus, L. S., Morse, D., Watanabe, Y., and Flores, D.: The advantages of demand over fixed rate pacing, Dis. Chest 8:16, 1968.
5. Bilitch, M., Cosby, R. S., and Cafferky, E. A.: Ventricular fibrillation and competitive pacing, New Eng. J. Med. 276:598, 1967.
6. Furman, S., and Escher, D. J.: Ventricular synchronous and demand pacing, Amer. Heart J. 76:115, 1968.
7. Furman, S., Escher, D. J., Solomon, N., and Kronteth, M.: Electrocardiographic manifestation of standby pacing, J. Thorac. Cardiovasc. Surg. 81:723, 1967.
8. Chatterjee, K., Sutton, R., and Davies, J. G.: Low intracardiac potentials in myocardial infarction as a cause of failure of inhibition of demand pacemakers, Lancet 1:511, 1969.
9. Goetz, R. H., Goldstein, J. A., Frater, R. W. M., and Berkovitz, B.: Demand pacing in intermittent heart block, J. A. M. A. 205:637, 1968.
10. Siddons, H., and Sowton, E.: Cardiac pacemakers, Springfield, Ill., 1967, Charles C Thomas, Publisher, chap. 9, p. 170.
11. Preston, T. A., Fletcher, R. D., Lucchesi, B. R., and Judge, R. D.: Changes in myocardial threshold. Physiologic and pharmacologic factors in patients with implanted pacemakers, Amer. Heart J. 4:235, 1967.

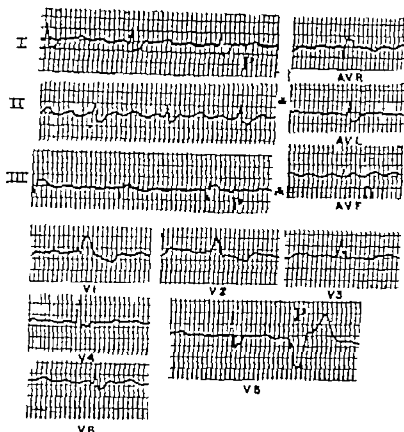


Fig 4 Patient II Electrocardiogram demonstrates atrial flutter with variable 3 1 to 4 1 atrioventricular response Pacemaker artifacts labeled *P* are noted in standard Leads I and III and a pacemaker induced ventricular response is noted in V_4 earlier than the preset interval of 1 000 msec.

normal situations will lower the myocardial resistance [11] The therapeutic response to steroids in the first case reported here and spontaneous full recovery over a 3 to 10 day period in the second case suggest to us that the stimulus electrode was functioning and the circuit was closed but that because of either edema or inflammation myocardial action potential was not delivered to the pulse generator implying an inability of the myocardium to generate at least 2 mv through the electrode. It is important to note that both patients had pericardial friction rubs at the time of their difficulties indicating some degree of inflammation at the electrode site Confirmation in fact, of power pack function in the first case was proved when we replaced the power pack and ruled out malfunction of the blocking circuit.

Our findings suggest that when the demand pacemaker is found to be functioning as a fixed rate unit, one must suspect entrance block and failure of inhibition of the generator by the QRS complex. The differentiation between a power pack malfunction and failure of the myocardium to deliver a signal to the power pack can be made with relative ease in the operating suite Isolation of the electrodes will allow oscilloscope measurement of the millivoltage generated to the power pack If this is lower than 2 mv entrance block to the pulse generator would be present and replacement of the power pack would be unnecessary

If entrance block is detected or suspected the use of corticosteroids as in our first case might be efficacious.

We do not know whether the synchronous type of demand pacemaker utilizing an epicardial sensing electrode will perform in a similar fashion but we suspect it might under similar circumstances.

Summary

A previously unreported malfunction of epicardial demand pacemakers is presented

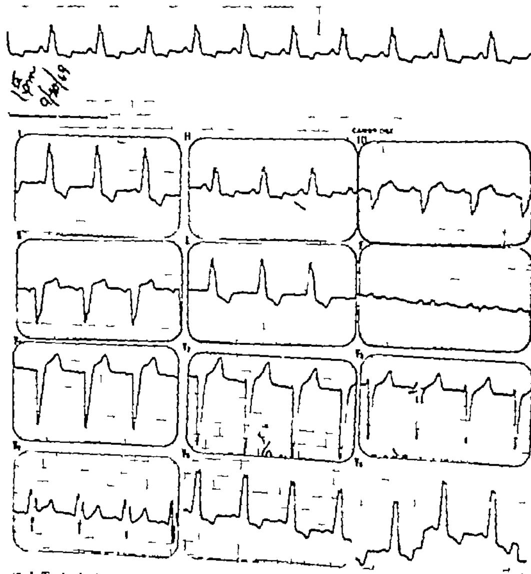


Fig. 1. Twelve-lead precatheterization electrocardiogram demonstrating left bundle branch block. The P R interval is 0.14 second.

...ne phosphatase, serum glutamine-oxalate transaminase, and serum protein. The serum cholesterol was 22. The initial chest roentgenogram demonstrated congestive heart failure and cardiomegaly. The electrocardiogram showed left bundle branch block with P R interval of 0.14 second (Fig. 1).

After prompt clearing of congestive heart failure following digitalis and furosemide administration, diagnostic cardiac catheterization was performed. During manipulation of No. 7 French bipolar pacing catheter in the right ventricle complete heart block occurred. Pervenous right ventricular pacing was immediately instituted. A tripolar catheter was inserted percutaneously into the femoral vein and

His-bundle electrograms were recorded from the area beneath the tricuspid valve, documenting the site of block as distal to the common bundle (Fig. 2). Administration of an intravenous infusion of isoproterenol (3 μg per minute) and intravenous atropine (1.0 mg) did not alter the block. Ventricular pacing was continued as the left and right heart catheterization was completed. Normal hemodynamic values were obtained (Table I). A left ventricular angiogram showed hypokinesis of the lateral left ventricular wall. Selective coronary arteriography demonstrated normal vascular supply to the heart with no evidence of coronary atherosclerosis. The septal arteries and atrioventricular nodal artery were well

Bundle-of-His recording of complete heart block during cardiac catheterization Electrophysiologic documentation of bilateral bundle branch block

Robert D Patton M.D **
Arun Bordia M.D **
Frederick Ballantyne M.D **
Gerald F Ryan M.D ***
Sidney Goldstein M.D F.A C C ****
Robert A Heinle M.D *****
Rochester N Y

Although right bundle branch block is a well known complication of right heart catheterization [1,2] complete heart block is unusual [3,4] In patients with pre-existing bundle branch block, block of the opposite bundle branch during catheterization may result in complete heart block [4] but only one patient previously reported has required insertion of a permanent pacemaker [5] This report documents a second instance of chronic heart block following cardiac catheterization and the first instance in which His-bundle electrograms confirmed the site of block as distal to the bundle of His.

Case report

A 55-year-old Caucasian plumber was admitted for cardiac evaluation two weeks after an illness characterized by cough, malaise, and myalgia. The patient noted the onset of dyspnea on exertion and orthopnea 10 days prior to admission. There was no past history of diabetes, hypertension, angina, heart murmur paroxysmal nocturnal dyspnea, or ankle edema, and no family history of heart disease or diabetes. He had consumed large amounts of beer and whiskey daily for many years, but had worked regularly and maintained good nutrition.

On examination the patient was afebrile. The blood pressure was 135/80 mm. Hg and the pulse was 78 and regular The neck veins were not distended. Bilateral basilar râles were present. The heart was enlarged 1 cm. to the left of the mid-clavicular line with a normal apical impulse. The heart sounds were of normal intensity and a third heart sound was present. No murmur or rub was present. The liver was enlarged 2 cm. below the right costal margin. No splenomegaly or ankle edema was present.

Pertinent laboratory values included a normal complete blood count, urinalysis, glucose tolerance test, blood urea nitrogen serum electrolytes, alka-

From the Cardiology Units, Rochester General Hospital and Strong Memorial Hospital, Rochester N Y
Supported in part by Grants HE 3500 and HE 3966 from the United States Public Health Service.
Received for publication Dec. 17 1969.
Reprint requests to Dr Patton, University of Rochester School of Medicine and Dentistry and Strong Memorial Hospital, 260 Crittenden Blvd., Rochester N Y 14620.
*Trainee in Cardiology Strong Memorial Hospital.
**Fellows in Cardiology Rochester General Hospital.
***Clinical Instructor in Medicine, University of Rochester Medical Center.
****Chief Cardiology Department, Rochester General Hospital, and Associate Professor of Medicine, University of Rochester Medical Center.
*****Assistant Professor of Medicine, University of Rochester Medical Center.

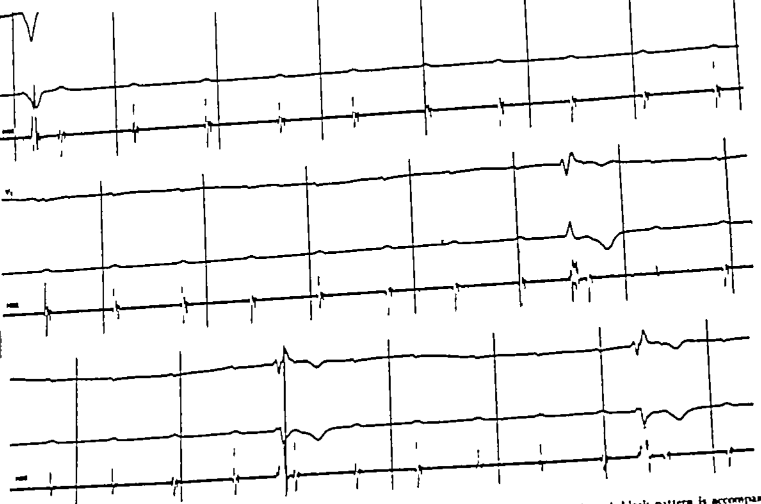


Fig. 3 Long, continuous rhythm trip 4 d ys after initial catheterization. Both V and Lead II are shown above, nd the His-bundle electrogram (*HBE*) is show below Immediately after pacing was discontinued slowly accelerating idioventricular focus occurred ith no preceding His spike. Note that the right bundle br nch block pattern is accompanied by left axis deviation i the second nd third pontaneous beats. The patient remained lert despit the slow hythm.

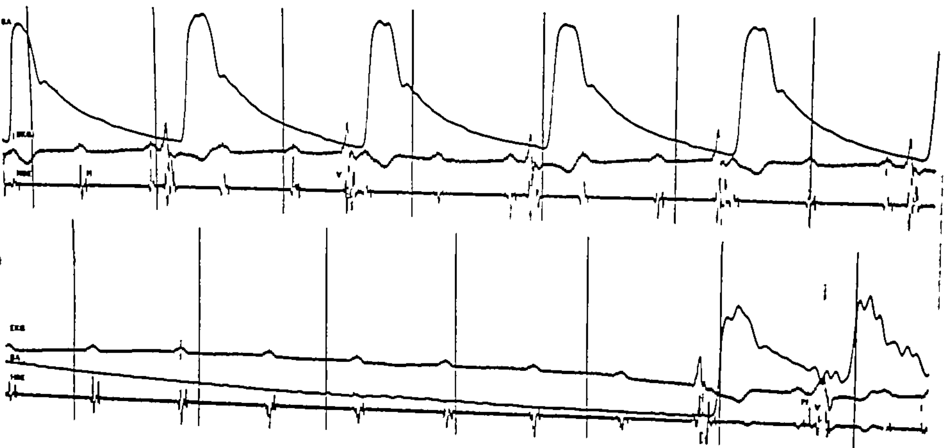


Fig. 2 Two rhythm strips during cardiac catheterization. O the pper trip ventricular pacing is present at 50 beats per minute (EKG Lead II) The brachial arterial pressure tracing is shown. A His-bundle electrogram shows a His spike following each atrial contraction. The bottom strip shows a 5.5 second period of asystole while the pacemaker was turned off The brachial arterial pressure dropped precipitously Atrial co tractions re gain followed by His-bundle spikes. The rterial pressure rose promptly o reinstitution of ventricular pacing *B* 1 = Brachial rtery pressure traci g *EKG* = Lead II rhythm trip *HBE* = His-bundle electrocardiogram Time lines are t one-second i tervals.

3. McIntosh, H. D.: Arrhythmias, Circulation 37-38 (Suppl. III):27, 1968.
4. Braunwald, E.: Deaths related to cardiac catheterization, Circulation 37-38 (Suppl. III):17, 1968.
5. Gault, J. H., Ross, J., Jr., and Braunwald, E.: Persistent atrioventricular dissociation with block and nodal rhythm after cardiac catheterization, Amer. Heart J. 71:690, 1966.
6. Stein, P. D., Mathur, V. S., Herman, M. V., and Levine, H. D.: Complete heart block induced during cardiac catheterization of patients with pre-existent bundle branch block, Circulation 34:783, 1966.
7. Scherlag, B. J., Lau, S. H., Helfant, R. H., Berkowitz, W. D., Stein, E., and Damato, A. N.: Catheter technique for recording His bundle activity in man, Circulation 39:13, 1969.
8. Damato, A. N., Lau, S. H., Helfant, R. H., Stein, E., Patton, R. D., Scherlag, B. J., and Berkowitz, W. D.: A study of heart block in man using His bundle recordings, Circulation 39:297, 1969.
9. Lepeschkin, E.: The electrocardiographic diagnosis of bilateral bundle branch block in relation to heart block, Progr. Cardiovasc. Dis. 6:155, 1964.

Table I Cardiac catheterization hemodynamic values

Parameters	*Findings*
Right atrium	3 mm Hg
Right ventricle	26/6 mm. Hg
Pulmonary artery	25/12 mean 18 mm Hg
Pulmonary capillary wedge	8 mm. Hg
Left ventricle	152/6 mm Hg
Brachial artery	162/86 mm Hg
Cardiac output	5.5 L./min.
Cardiac index	2 1 L./min.

visualized From the catheterization data it was not possible to distinguish between a resolving myocarditis and alcoholic cardiomyopathy

Heart block persisted despite 40 mg of prednisone daily and a repeat bundle-of His recording four days later showed an idioventricular rhythm from multiple ventricular foci. No evidence of atrioventricular conduction was noted the area of block remained below the bundle of His (Fig 3) Long symptomatic periods of asystole were noted when the pacemaker was discontinued. When conduction failed to improve, a permanent demand transvenous pacemaker (Medtronic No 5811) was inserted with subsidence of the patient's symptoms.

Discussion

In a review of 12 367 cardiac catheterization procedures development of heart block was noted in seven patients[1,4] The only adult patient was a 51 year-old woman with rheumatic heart disease a d left bundle branch block who developed complete heart block during catheter manipulation in the right ventricular outflow tract. Sinus rhythm returned 75 minutes later[4] A 13 year-old girl with tetralogy of Fallot and dextroposition of the heart included in this series was reported separately[5] During cardiac catheterization she developed atrioventricular dissociation with idioventricular rhythm and occasional captured beats Her arrhythmia persisted and nine months later a permanent pacemaker was inserted She represents the only patient reported previously with permanent heart block. In another series of five patients with pre-existent bundle branch block transient complete heart block occurred during cardiac catheterization[6] In four patients with left bundle branch block complete heart block occurred during right heart catheterization The fifth patient with right bundle branch block developed complete heart block during left heart catheterization

The cases cited above are consistent with the hypothesis that complete heart block occurring in patients with pre-existing bundle branch block is due to block of the opposite bundle branch induced by the catheter during catheterization In our patient, His-bundle electrograms on two separate occasions demonstrated His spikes following each atrial complex without relationship to the spontaneous or paced ventricular beat These findings are consistent with bilateral bundle branch block and add additional support to the hypothesis presented above In contrast to the above-mentioned patient who required a permanent pacemaker but in whom some atrial captured beats occurred our patient failed to demonstrate any evidence of ventricular capture Incomplete right bundle branch involvement such as a prolonged P R interval[8] was not present on the electrocardiogram prior to cardiac catheterization

The experience with this patient supports the use of a standby pacemaker in patients with bundle branch block when catheter manipulation will occur in the region of the opposite bundle branch

Summary

A 55-year-old man with pre-existing left bundle branch block developed complete heart block during right heart catheterization This patient represents the second patient in whom this complication required permanent pacemaker and the first patient in whom bundle-of His electrograms localized the area of block to the conduction system distal to the His bundle

The authors wish to thank Miss N ncy Rae for her secretarial assistance and especially Dr Paul N Yu for his helpful review

REFERENCES

1 Fraser R. S., Macauley W D and Rowall R. E.: Arrhythmias induced during I tracardiac catheterization AMER. HEART J 61:459 1962.
2 Wennevold, A. Christiansen, J and Lindeneg, O : Complications in 4 413 catheterization of the right side of the heart, AMER. HEART J 69:173 1965.

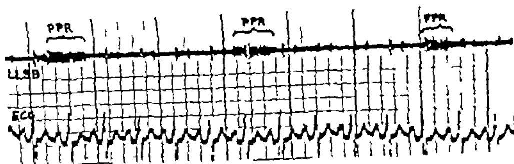


Fig. 1. Pleuropericardial friction. There is pericardial rub in systole and (fainter) in diastole. A loud pleuropericardial rub (PPR) appears at peak inspiration (dash marker at bottom of ECG).

(combined rubs).[6] In many cases the friction sounds in acute pericarditis cease with the accumulation of a significant amount of effusion fluid. Why they frequently do not disappear despite even very large effusions is not clear. Indeed, a rub present during an effusion may even disappear after paracentesis.[7] Perhaps the audible rub in such patients is exopericardial and requires increased intrapericardial pressure to maintain friction between the parietal pericardium and the pleura or chest wall. Pleuropericardial rubs (Fig. 1) may be due to primarily pleural inflammation, pericardial inflammation, or simultaneous involvement of both, and are distinguished by having respiratory as well as cardiac periodicity.

Phonically, rubs are composed of mixed (mainly high) frequency vibrations which are usually sufficiently distinctive in auscultatory quality and in clinical setting to escape confusion with most murmurs. They vary in intensity from a very subtle distant "scrape" or set of "scrapes" to grating, scratching, or creaking noises which often appear to "obliterate" or give the illusion of "going through" the heart sounds, sometimes with a startling impression of superficiality. Unlike most murmurs, rubs often tend to change quite noticeably with respiration and body position. They also do not respect the conventional murmur zones of maximum intensity and radiation. Because of their frequency characteristics, pericardial rubs are best heard with the stethoscope diaphragm and tend to vary markedly with varying pressure of the bell of the stethoscope. During acute pericarditis, rubs may migrate and show short term changes in intensity and phase structure, and may disappear for variable periods.

Endopericardial rubs occur with acute and subacute inflammation of the visceral pericardium, are rather monotonal over any short period, and tend to disappear with the resolution of an acute process. *Exopericardial rubs* result from severe acute pericarditis, particularly if due to direct extension from adjacent inflammation or tumor implantation. They also occur after pericardiectomy and pericardiotomy in association with either constrictive or nonconstrictive pericardial scarring and with pleuritis (*pleuropericardial rub*). When due to subacute or chronic processes, they can last indefinitely. They are more likely than endopericardial rubs to change with respiration, to seem quite superficial, and to show a tendency to a musical quality.

The true incidence of pericardial rubs is, of course, uncertain and must vary depending on patient population and the frequency and diligence of auscultation. Evanescent rubs during acute myocardial infarction, for example, may be detected because of the frequency of auscultation, which would also be true in most cases of painful acute pericarditis. The far from rare pericardial rubs of rheumatoid arthritis, on the other hand, are generally discovered by accident, since symptomatic pericarditic syndromes are not common in this very common disease.[3,4]

Rubs have classically been designated as "to-and-fro," i.e., biphasic phenomena. Some, indeed, are. However, this blanket designation belongs to the recently deceased auscultatory era which was char

Review

Acoustic phenomena in pericardial disease

*David H. Spodick, M.D.**
Boston, Mass.

A wide variety of auscultatory phenomena accompany disorders of the pericardium. Most of these are direct or indirect consequences of the pericardial process itself. Some are caused by disease of the heart valves and chordae tendineae having the same origin as an accompanying acute or adhesive pericarditis. A few are due to the natural coincidence of myocardial or valvular disease with unrelated pericarditis. The auscultatory phenomena fall into five categories: rubs, altered heart sounds, effect of pneumohydropericardium (spontaneous or induced), murmurs, and clicks.

Effect of pneumohydropericardium

To take the least important first, we may quickly dismiss the findings in pneumohydropericardium. These depend upon the relative amounts of gas and fluid in the pericardial sac. With a few milliliters of gas a metallic tinkle synchronous with systole and occasionally with both systole and early diastole may be heard. With large amounts of gas a churning, splashing millwheel sound (*bruit de la roue hydraulique*) is audible. Gas bacillus infections of the pericardium are quite rare, while spontaneous pneumohydropericardium is occasionally seen due to pericardial erosion in disease of a contiguous organ (usually a gastric or esophageal neoplasm). Iatrogenic pneumohydropericardium is far more common. It is our practice to replace fluid removed by paracentesis quantitatively—i.e., milliliter for milliliter—with air if tolerated by the patient.[1,2] (Of course at conditions of body temperature and pressure the air volume in the pericardial sac probably is different.) Under these conditions we have frequently heard both the metallic sounds after the first few milliliters and later the millwheel sounds. One other iatrogenic phenomenon may be heard if one listens to the precordium as air is being introduced: the bubbling sound of air entry through fluid.

Rubs

The pericardial rub or friction sound is the hallmark of acute pericarditis and frequently is audible in subacute and even chronic pericardial disease. Pericardial rubs are considered to be due to friction between inflamed, scarred, or tumor-invaded surfaces of the visceral pericardium (endopericardial rubs) or between the parietal pericardium and the adjacent pleura or chest wall (exopericardial rubs) or both

From the Cardiology Division, Medical Service, Lemuel Shattuck Hospital, and the Department of Medicine, Tufts University, Boston, Mass.

Presented at the Symposium on the Pericardium in Health and Disease, University of Kentucky Medical Center, Lexington, Ky., Sept. 25 and 26, 1969.

Address for reprints: Cardiology Division, Lemuel Shattuck Hospital, 170 Morton St., Boston, Mass. 02130.

*Director, Cardiology Division, Lemuel Shattuck Hospital; Associate Professor of Medicine, Tufts University; Lecturer in Medicine, Boston University.

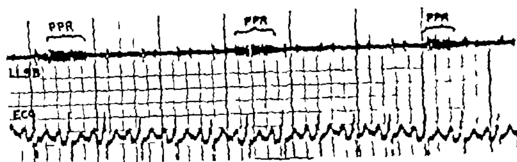


Fig. 1 Pleuropericardial friction. There is pericardial rub in systole and (fainter) in diastole. A loud pleuropericardial rub (*PPR*) appears at peak inspiration (dash marker at bottom of ECG)

(combined rubs) In many cases the friction sounds in acute pericarditis cease with the accumulation of a significant amount of effusion fluid. Why they frequently do not disappear despite even very large effusions is not clear. Indeed a rub present during an effusion may even disappear after paracentesis. Perhaps the audible rub in such patients is exopericardial and requires increased intrapericardial pressure to maintain friction between the parietal pericardium and the pleura or chest wall. Pleuropericardial rubs (Fig. 1) may be due to primarily pleural inflammation, pericardial inflammation, or simultaneous involvement of both and are distinguished by having respiratory as well as cardiac periodicity.

Phonically, rubs are composed of mixed (mainly high) frequency vibrations which are usually sufficiently distinctive in auscultatory quality and in clinical setting to escape confusion with most murmurs. They vary in intensity from a very subtle distant "scrape" or set of scrapes to grating, scratching, or creaking noises which often appear to "obliterate" or give the illusion of "going through" the heart sounds, sometimes with a startling impression of superficiality. Unlike most murmurs, rubs often tend to change quite noticeably with respiration and body position. They also do not respect the conventional murmur zones of maximum intensity and radiation. Because of their frequency characteristics, pericardial rubs are best heard with the stethoscope diaphragm and tend to vary markedly with varying pressure of the bell of the stethoscope. During acute pericarditis, rubs may migrate and show short term changes in intensity and phase structure and may disappear for variable periods.

Endopericardial rubs occur with acute and subacute inflammation of the visceral pericardium, are rather monotonal over any short period and tend to disappear with the resolution of an acute process. *Exopericardial rubs* result from severe acute pericarditis, particularly if due to direct extension from adjacent inflammation or tumor implantation. They also occur after pericardiectomy and pericardiotomy in association with either constrictive or nonconstrictive pericardial scarring and with pleuritis (*pleuropericardial rub*). When due to subacute or chronic processes, they can last indefinitely. They are more likely than endopericardial rubs to change with respiration, to seem quite superficial, and to show a tendency to a musical quality.

The true incidence of pericardial rubs is, of course, uncertain and must vary depending on patient population and the frequency and diligence of auscultation. Evanescent rubs during acute myocardial infarction, for example, may be detected because of the frequency of auscultation, which would also be true in most cases of painful acute pericarditis. The far from rare pericardial rubs of rheumatoid arthritis, on the other hand, are generally discovered by accident, since symptomatic pericarditic syndromes are not common in this very common disease.[3,4]

Rubs have classically been designated as "to-and-fro," i.e., biphasic phenomena. Some, indeed, are. However, this blanket designation belongs to the recently deceased auscultatory era which was char

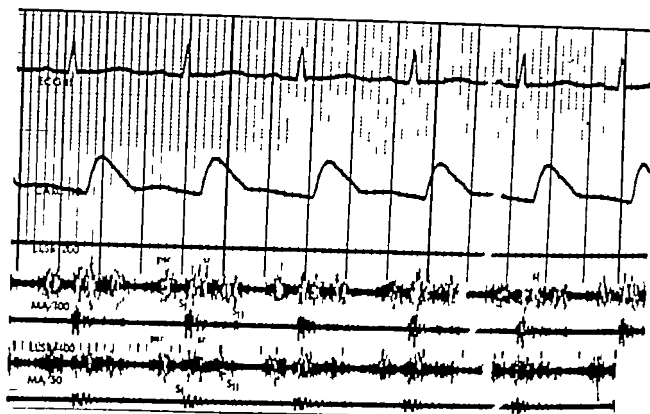


Fig 2 Biphasic (truly "to-and fro") pericardial friction. The rub is composed of vibrations during ventricular systole (*sr*) and atrial systole (*psr*)

Table I Characteristics of pericardial friction rub in 50 consecutive cases

Phases	*No. of cases*	*Percentage of series*	*Rate/min (No of cases)*			
			60-79	80-99	100-119	120-140
3	29	58	3	14	8	4
2	12	24	2	7	2	1
1	9	18		2	2	5
	50	100				

acterized for example by nondiscrimination of the components of the second heart sound and hazy distinction between the notation for heart sounds and auscultatory areas. In a search for a more accurate picture of the phase structure of pericardial rubs we studied 50 consecutive patients at the time pericarditis was discovered[4] Three observers recorded their findings independently of one another with regard to phasic components of the rubs palpability auscultatory areas where best heard and relationship to respiratory phases. There was unanimity on auscultatory findings in 44 cases phonocardiograms taken for teaching interest in this group confirmed the bedside results. In each of six cases in which one or more examiner dissented phonocardiograms disclosed the phasic timing of the rub components. Only a quarter (24 per cent) of the rubs could be called "to-and fro" (Fig 2) and these had several biphasic patterns (Table I) Fifty-eight per cent

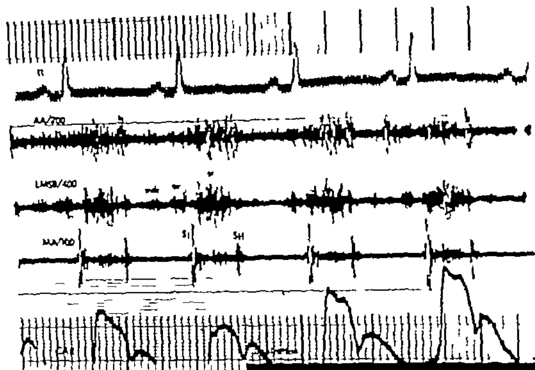


Fig. 3 Triphasic pericardial friction. Rub vibrations are seen during atrial systole (*a*), ventricular systole (*vs*) and in middiastole (*mdr*).

were triphasic, occurring in atrial systole ventricular systole and early ventricular diastole (Fig 3) Nine (18 per cent) were monophasic (Fig 4) Thus, triphasic pericardial friction sounds are the rule and monophasic rubs are almost as frequent as biphasic ("to-and fro") rubs.

Eleven of the 50 rubs were palpable. Forty-seven rubs were best heard adjacent to the left midsternum mainly next to the left lower to-midsternal border (Table II) This was probably because of a lack of intervening lung in that zone. There was no respiratory phase predilection i.e. one third each were heard better in inspiration or expiration or equally well heard in both phases.

It is to be emphasized that this study was limited to the earliest detection of pericardial rubs and to patients for whom we could quickly assemble three auscultators concerned with this prospective study. No formal attempt was made to follow up rub fluctuations and disappearance times in this series.

Table II Additional features of rubs in 50 cases

Feature	*No. of cases*
Palpability	11
Auscultatory areas where best heard	
Left lower to left midsternal border	42
Left upper to left midsternal border	5
Apex	2
Right midsternal border	1
Relation to respiratory phases:	
Equal in inspiration and expiration	17
Louder in inspiration	18
Louder in expiration	15

Murmurs

Since by definition, murmurs are auscultatory phenomena related to blood flow through orifices and vessels, they can be caused by pericardial lesions only when the pericardial process is sufficiently intense as to involve an orifice or a vessel.

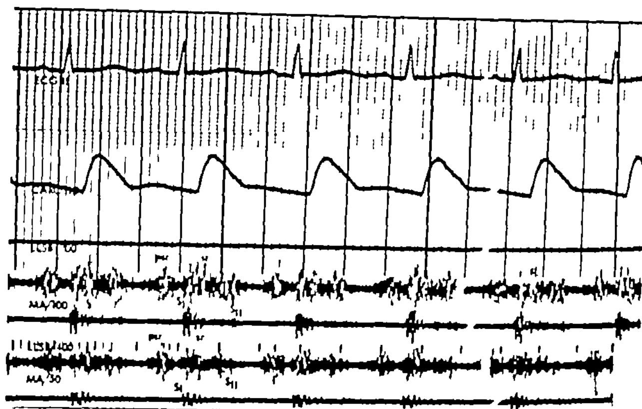


Fig. 2 Biphasic (truly "to-and fro") pericardial friction. The rub is composed of vibrations during ventricular systole (*sr*) and atrial systole (*psr*)

Table I Characteristics of pericardial friction rub in 50 consecutive cases

Phases	*No. of cases*	*Percentage of series*	*Rate/min (No of cases)*			
			60-79	80-99	100-119	120-140
3	29	58	3	14	8	4
2	12	24	2	7	2	1
1	9	18		2	2	5
	50	100				

acterized for example by nondiscrimination of the components of the second heart sound and hazy distinction between the notation for heart sounds and auscultatory areas. In a search for a more accurate picture of the phase structure of pericardial rubs we studied 50 consecutive patients at the time pericarditis was discovered[4] Three observers recorded their findings independently of one another with regard to phasic components of the rubs palpability auscultatory areas where best heard and relationship to respiratory phases. There was unanimity on auscultatory findings in 44 cases phonocardiograms taken for teaching interest in this group confirmed the bedside results. In each of six cases in which one or more examiner dissented phonocardiograms disclosed the phasic timing of the rub components. Only a quarter (24 per cent) of the rubs could be called "to-and fro" (Fig 2) and these had several biphasic patterns (Table I) Fifty-eight per cent

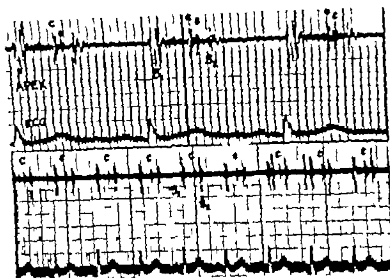


Fig. 5 Systolic click. The bottom tracing (25 mm. per second recording speed) shows mid- to late systolic click (c) in patient with pericardial adhesions and probable mild mitral regurgitation. The top tracing (75 mm. per second) reveals the click to have two component sets of vibrations and to accompany a parasystolic murmur. (From Spodick, D. H. Chronic and constrictive pericarditis, New York and London, 1964, Grune & Stratton, Inc.)

heave pericarditis and are strictly the result of valvular and myocardial impairment. An unusual exception to the innocence of rheumatic pericardial adhesions is the occurrence of severe rheumatic mediastinopericarditis, which has been known to involve the pulmonary artery sufficiently to cause harsh ejection murmurs and accentuation of IIp—the findings of supravalvular pulmonic stenosis.

In constrictive pericarditis, systolic murmurs have been noted in up to one third of various series.[1] Those due to coincidental intrinsic heart disease (category I A) tend to be loud. On the other hand faint systolic murmurs in the absence of valve abnormalities may be due to functional impairment of the myocardium or valves, rather than direct encroachment by the pericardial scar. Diastolic murmurs have rarely been noted under the same circumstances and with normal valves.[4-11]

In the last category (II) are murmurs due to constrictive pericardial scarring and calcification. These are quite uncommon. The pericardial process either narrows the valve orifices by compression or actually physically disrupts the valve. Atrioventricular groove constriction, for example, has produced mitral and tricuspid stenosis, with murmurs indistinguishable in quality and timing from those of valve disease and behaving similarly during respiration and administration of amyl nitrite.[1,12] Systolic murmurs of relative aortic and pulmonic stenosis have been noted as well as those of infundibular and supravalvular stenosis of the same structures.[1,13,14] Occasional patients will have murmurs and gradients demonstrable at catheterization but without apparent involvement of the valve.[7] These could be due to local variability in the constrictive process,[1] but the mechanism is not certain.

Clicks

Clicks are high frequency, fairly discrete vibrations which are more common in phonocardiograms than in ordinary auscultation[1] (Fig. 5). They often resemble in timbre the ejection sounds and opening snaps of stenosed valves. Those traditionally associated with pericardial disease tend to occur in mid to late systole; thus, timing distinguishes them from the semilunar valve ejection clicks of early systole and the opening snaps of A-V valves which follow the second heart sounds. (The isodiastolic pericardial vibration of

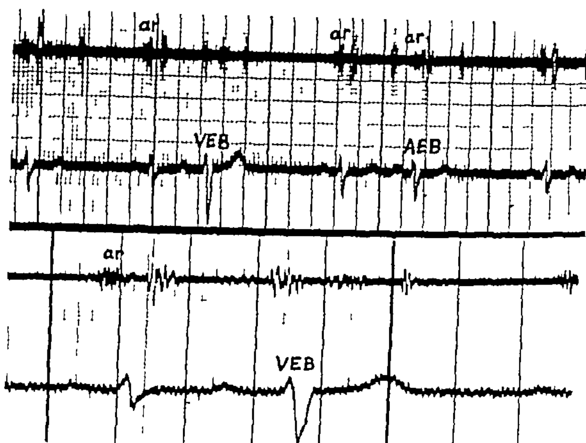


Fig 4 Monophasic pericardial friction Top tracing recorded at 25 mm per second bottom tracing at 75 mm per second. Rub vibrations are confined to atrial systole and follow the P wave of the ECG both in sinus beats and in atrial ectopic beats (AEB) they are absent before ventricular ectopic beats (VEB) (From Spodick D H New Eng J Med 278 1201 1968)

Thus murmurs as a direct consequence of pericarditis are difficult to demonstrate as such and in practice occur only when a cicatricial pericardial process involves a valve ring or locally narrows a portion of the heart the pulmonary artery or the aorta.[3] They are therefore rare Schrire and associates[7] for example found only murmurs associated with unrelated valve disease in 220 consecutive patients with constrictive pericarditis. We may outline the pathogenesis of murmurs in pericardial disease as follows

Murmurs in pericardial disease

I DUE TO HEART DISEASE
- A Not associated with the pericardial process.
- B Associated with the pericardial process.

II DUE TO CONSTRICTIVE PERICARDIAL SCARRING AND CALCIFICATION

In the first category (I A) we have the coincidence of congenital or acquired heart lesions with pre-existing or subsequent pericarditis. Examples of these in constrictive pericarditis include[3] rheumatic lesions—mitral stenosis mitral regurgitation aortic stenosis and tricuspid stenosis and congenital lesions—atrial septal defect ventricular septal defect pulmonic stenosis and aortic coarctation

The next category (I B) includes intrinsic heart lesions in the presence of either acute or healed pericarditis having a common origin Sometimes this is due to bacterial endocarditis (particularly with aortic valve involvement[8]) More frequent is the association of rheumatic valvulopathy with adhesive pericarditis When the latter is the residuum of rheumatic pericarditis it has never been convincingly demonstrated as functionally important from the standpoint of constriction of the cardiac chambers.[3] Thus, all the murmurs caused by rheumatic heart disease may be found in patients with ad

tend to make the heart sounds more remote. This may also be true of thick scar although it would be difficult to separate the effects of dense adhesions and fibrous from the dynamic effects of any associated valve disease or constrictive process. Moreover it is possible that thick fibrous tissue by itself might actually improve the coupling of the myocardium to the chest wall and transmit heart sounds better than the air-filled lung parenchyma. This hypothesis has not been tested so that fluid is the only more or less certain insulating medium although it is not rare even with fairly large nontamponading pericardial effusions to find surprisingly clear heart sounds of apparently normal or near-normal intensity.[1]

Hemodynamic changes common to both cardiac tamponade and constrictive pericarditis tend to have similar effects on the amplitude of the first heart sound and of the components of the second heart sound. Decreased stroke volume and impairment of the contractile properties of the myocardium and their effects on flow velocity probably account for diminution of S_I and the aortic component of S_{II} (II_A) (Fig. 6). Increased pulmonary artery pressures particularly in constriction are associated with accentuation of the pulmonic component (II_P) relative to II_A. Sometimes II_P has, in fact, seemed absolutely increased on auscultation although this may have been due to confusion with a very early abnormal S_{III} which can be well transmitted to the left upper sternal border in patients with constriction. Persistence of pericardial rubs during tamponade and subacute or even chronic, constriction will of course tend to alter the perception of any contiguous heart sounds.

Auscultatory findings are better understood in constrictive pericarditis than in cardiac tamponade and in intermediate syndromes in which cardiac compression is associated with both scar and fluid (e.g. many of the cases of chronic pericardial effusion some cases of subacute and chronic constriction). Constrictive pericarditis alters the normal heart sounds and produces new sounds via the combined results of hemodynamic abnormalities, diminished ventricular volumes and reduced myocardial compliance. A fourth heart sound (S_{IV}) is rarely heard (in patients with sinus rhythm) and can be ascribed to the high resistance to ventricular filling following atrial systole.[3]

A loud abnormal early diastolic sound (EDS" S_{III}) is the hallmark of constrictive pericarditis (Fig. 7). Its occurrence is associated with the abrupt halt of rapid filling in early diastole owing to decreased ventricular compliance small ventricular volume and high filling pressure. The *EDS* usually occurs from 0.10 to 0.15 second after II_A; its relative timing is analogous in behavior to that of opening snaps, i.e., the greater the filling pressure and the less the myocardial compliance the closer the EDS will be to II.[4] This sound may be the only loud heart sound and may be misinterpreted as S_I if the rate is fast and particularly if there is an early diastolic thrust of the chest wall which can be mistaken for the apex beat. Some very early abnormal sounds can be quite high-pitched and may suggest a mitral or tricuspid opening snap. Patients with heavy calcification may have an especially loud and sharp EDS, but this



Fig. 7 Abnormal early diastolic sound (*EDS*) in constrictive pericarditis, coinciding approximately with the exaggerated y trough of the jugular venous pulse. (From Spodick, D. H.: Chronic and constrictive pericarditis, New York and London, 1964, Grune & Stratton, Inc.)

Lian is a phonocardiographic oddity of dubious origin [8])

Clicks associated with pericardial disease are found with both constrictive and nonconstrictive pericardial scarring A systolic click plus the first and second heart sounds and an abnormal early diastolic sound produces a quadruple or train track rhythm In the absence of an S_{III} a so-called systolic triple rhythm or *bruit de triolet* results. The origin of the systolic clicks in uncomplicated constrictive pericarditis is uncertain although they have been ascribed to movements between articulating calcific plaques and sudden tension on discrete pericardial adhesions during systole The latter mechanism is also the traditional explanation for the systolic clicks of nonconstrictive pericardial adhesions It is far more likely that most clicks are produced within the heart by lesions of the valvular apparatus particularly rheumatic mitral disease When for example one or more chordae tendineae are relatively longer than other shortened fibrosed chordae [17] uneven distribution of tension during systole may produce a click Similarly clicks may result from the mid to late-systolic arrest of a mitral cusp everting into the atrium owing to disruption of papillary muscle mechanics.

Heart sounds

Abnormalities of the heart sounds due to pericardial disease are the results of insulation of the heart, hemodynamic abnormalities or changes in myocardial compliance singly or in combination These may be outlined as follows

Effects of pericardial disease on the heart sounds

A INSULATION effusion fluid ? thick scar both

⟶ decreased amplitude

B HEMODYNAMIC CHANGES tamponade constriction

1 Decreased stroke volume + impaired contraction
⟶ decreased S_I and II_A
2 Increased PA pressure
⟶ increased II_P

C CONSTRICTIVE PERICARDITIS results of hemodynamic abnormalities + decreased compliance + small ventricle

1 ? S_{IV}
2 S_{III} abnormal early diastolic sound (EDS)
3 Respiratory behavior of S_{II}
(a) relatively fixed split *or*
(b) early II_A abruptly with inspiration (patients with pulsus paradoxus)

Insulation of the heart by fluid should

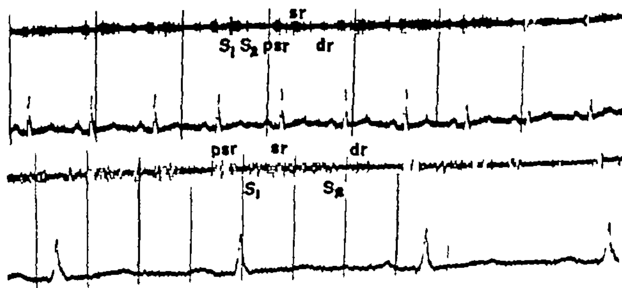


Fig. 6 Diminished heart sounds (S S_2) and persistence of *triphasic pericardial rub* (*psr sr d*) in presence of large (> 750 ml) pericardial effusion. Recording speeds: top, 25 mm. per second bottom, 75 mm. per second. (From Spodick, D H Progr Cardiovasc. Dis. 10:64 1967)

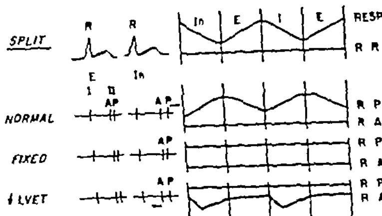


Fig 9 Respiratory splitting of the second heart sound ts forms in constrictive pericarditis compared with normal split. Abbreviations *I* = Inspiration *Ex* = expiration *RESP* = respiratory curv *R* = pe k of R wave of ECG *R R* = cycle length measured from ECG R w es *I* = first heart sound; *II* = second heart sound *A* = aortic component of *II* *P* = pulmonic component of II. The top diagram hows the R R interv l to be constant hile respiration aries phasically Second diagram Normal spl ttin —the timing of *P* (*R P*) varies hile the timing of *A* (*R A*) is virtually fixed Third diagram Fixed splitting—both R I nd R \ do not change with respiratory phases Bottom diagram Early *A* R P is fixed hile R A decre ses bruptly after the onset of inspiration owing to decreased left ventricular ejection time (↓ LVET).

the reduced ventricle of constriction filling is characterized by a forceful expansion which halts abruptly in early diastole and is *monophasic* i e., lacking the slow filling phase so that S_{III} probably occurs at the peak of ts volume curve. Thus, while it is likely that the abnormal EDS of constrictive pericarditis can be wholly or partly due to whatever produces the normal S_{III} and the S_{III} gallop of mitral regurgitation the appropriate experiment to specifically test this is lacking

Two patterns of splitting of the second heart sound (S_{II}) may be found in constrictive pericarditis (Fig 9) In the absence of a definite pulsus paradoxus there is little change with respiration so that one hears an almost fixed split. This is due to virtual immobil ty of the pulmonic component (II_P) in contrast to the normal situation in which delay of II_P is responsible for most of the inspiratory widening This may be ascribed to minimal or absent change in right ventricular stroke volume lead ng to virtual fixation of the duration of right ventricular systole during respiratory changes.

The peculiar form of S_{II} splitting occurring in some cases of constrictive pericard tis has been investigated by Beck, Schrire and Vogelpoel[11] This occurs within one beat after the onset of in piration In common with the cases of fixed split ting II_P is virtually fixed (and for the same reason) but the aortic component of S_{II} (II_A) abruptly moves inward —i.e oc curs earlier by about 30 msec. Tl is hap pens in cases with well marked in piratory diminution of the arterial pulse both the maximum fall in arterial pressure and the earliest timing of II_A occur one beat after the onset of inspiration followed by par allel restoration of both phenomena to their expiratory levels (Fig 9) Tl ese cases are uncommon since well marked *pulsus paradoxus* is the exception in con striction[1] Whatever its mechanism this *behavior of II* reflects shortened left ventricular ejection time owing to under filling of the left ventricle in such patients.

REFERENCES

1. Spodick, D H. Acute cardiac tamponade pathophysiology diagnosis nd management, Progr Cardiovasc Dis 10:64 1967
2. Spodick, D H Electric alternation of the heart. Its relation to the kinetics and physiology of the heart during cardia tamponade, Amer J Cardiol. 10 155 1962
3. Spodick, D H : Chronic and constrictive pericarditis, New York and London, 1964 Grune & Stratton, Inc.
4. Spodick, D H. Pericardial friction charac teristics of pericardial rubs in fifty consecutive

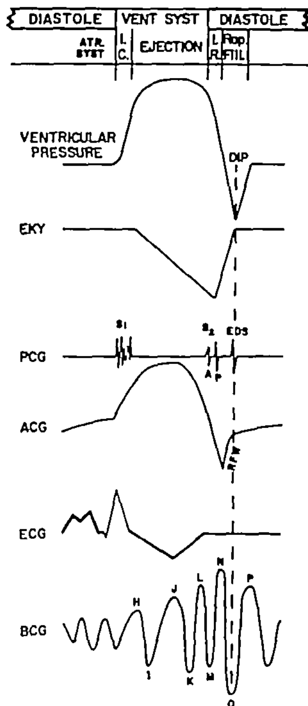


Fig 8 Graphic correlates of the abnormal early diastolic sound (*EDS*) of constrictive pericarditis. Top to bottom phases of the cardiac cycle ventricular pressure electrokymogram phonocardiogram apexcardiogram electrocardiogram ballistocardiogram. (From Spodick, D H Chronic and constrictive pericarditis, New York and London 1964 Grune & Stratton, Inc.)

is probably due to markedly reduced compliance rather than the presence of calcification Intensity like timing appears to vary directly with the abruptness with which ventricular expansion halts, since louder third sounds are correlated with greater filling pressures and atrioventricular gradients and with the steepness of the reascent from the typical protodiastolic dip of the ventricular pressure curve Graphic correlates of the EDS (Fig 8) are (1) apexcardiogram—the peak of the rapid filling wave (2) ballistocardiogram—EDS is preceded by sharp left footward and ventral motion and *followed* by larger right headward and posterior forces (3) jugular venous pulse —EDS occurs before or at the *y* trough (4) ventricular pressure curve—EDS occurs between the nadir of the protodiastolic dip and the end of the upstroke from the dip The exact mechanism of the EDS is not settled Investigations demonstrating the mechanism of the normal S_{III} or the S_{III} of mitral regurgitation may bear on this phenomenon Thus Luisada's group[18] has shown that a normal S_{III} coincides with return to the baseline of dP/dt i e the point at which the rates of filling and relaxation of the ventricle become equal this occurs during rapid inflow but before the peak of the volume curve and coincides with the nadir of mural tension Therefore the normal S_{III} occurs at transition from active relaxation to passive distention Dock and co-workers[19] have presented evidence for retensing of the atrioventricular valves as at least part of the mechanism for the abnormal EDS the ballistocardiographic correlation of the EDS noted above is an important part of this evidence the direction of ballistic forces suggests a reflux wave focused on the A V valves.[19] Dayem and Raftery's[20] observation that postoperative recurrence of mitral regurgitation with a prosthesis replacing the valve is not accompanied by an S_{III} suggests that the valve leaflets are indeed needed to produce the sign To the extent that findings in the large volume ventricle of mitral regurgitation are applicable to the small ventricle of constriction this lends support to the valvular hypothesis. But it is noteworthy that a *normal* S_{III} occurs before the peak of the ventricular volume curve and may be *followed* by a ventriculoatrial gradient[18] and this may also be true in mitral regurgitation However in

Ultrastructural changes in renal arterioles and juxtaglomerular cells in hypertension

Edwin R. Fisher, M.D.
Pittsburgh, Pa.

Arteriolar hyalinosis is a well-recognized pathologic manifestation of arterial hypertension. It is also becoming increasingly apparent that this alteration may be encountered in tissues of normotensive individuals, particularly those with advanced age. In the latter, the lesions are usually milder but qualitatively indistinguishable from those observed in hypertensive subjects.[1,2] This information allows for the hypothetical consideration that perhaps the hypertensive state aggravates the process of arteriolar hyalinosis—a lesion indigenous to arteriolar vasculature. In this light one might also speculate as to the possible analogous effects of diabetes, progressive systemic sclerosis, and gout on the development of such arteriolar alterations, since individuals with these disorders frequently exhibit this angiopathy as well as a predilection for the hypertensive state. In order to support such a contention, it became readily apparent that information concerning the identity and hopefully the pathogenesis of arteriolar hyalinosis would be highly desirable. To accomplish this we have resorted to electron-microscopic study of the arterioles in renal biopsies from patients with essential hypertension, progressive systemic sclerosis, and gout, and adolescents and young adults as well as older persons with diabetes. The use of renal tissue for this purpose was selected not only because of its accessibility as compared for instance with the arterioles of adrenal capsule which also frequently reflect arteriolar change particularly in the presence of hypertension but also because of the ancillary yet pertinent information concerning the pathogenesis of hypertension which might be provided by the evaluation of the juxtaglomerular apparatus in such kidneys. Although abundant quantitative information concerning juxtaglomerular cell activity and its relationship to renal or renovascular hypertension mediated through the renin-angiotensin aldosterone system is available from experimental as well as limited numbers of human studies, no systematic, qualitative observations concerning these structures in man have been performed.

The possibility also arose that results of such a study might provide pertinent information concerning the nature of hypertension characterizing such clinical states as toxemia of pregnancy which heretofore might be justifiably regarded as doubtful or unknown.

Methods

All renal tissue was obtained by percutaneous renal biopsy using a Menghini needle. Of the 11 patients with essential

From the Departments of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, Pa. 15213, and the Veterans Administration Hospital, Pittsburgh, Pa. 15240.
Supported by United States Public Health Service Grant C-4131.

prospectively studied patients, New Eng J Med 278:1203 1968.

5. Spodick, D H Acute pericarditis, New York and London 1959 Grune & Stratton Inc.
6. Cathcart E. and Spodick D H Rheumatoid heart disease. *A study of the incidence and nature of cardiac lesions in rheumatoid arthritis* New Eng J Med 266:959 1962
7. Schrire V Gotsman, M S and Beck W Unusual diastolic murmurs in constrictive pericarditis and constrictive endocarditis, AMER HEART J 76:4 1968.
8. Gouley B A Constriction of the pulmonary artery by adhesive pericarditis, AMER. HEART J 13:470 1937
9. Christian, H A. Pericardial constriction Trans. Ass. Amer Physicians 50:288 1935
10. Deterling R. A and Humphreys, G H Factors in the etiology of constrictive pericarditis, Circulation 1:30 1955
11. Harrington, S W and Barnes, A R Diagnosis and surgical treatment of chronic constrictive pericarditis, Southern Surg. 9:159 1910
12. Paul O Castleman, B and White, P D Chronic constrictive pericarditis: a study of fifty three cases, Amer J Med Sci. 216:361 1948
13. Beck, C S and Cushing E. H Circulatory stasis of intrapericardial origin; clinical and surgical aspects of Pick's syndrome J.A.M.A. 102:1543 1934
14. Levine S. A. and Harvey W P Clinical auscultation of the heart, ed 2 Philadelphia, 1959 W B Saunders Company
15. McGaff C. J., Haller J A., Leight, L, and Towery B T: Subvalvular pulmonary stenosis due to constriction of the right ventricular outflow tract by a pericardial band, Amer J Med. 34:142 1963
16. Mounsey P Annular constrictive pericarditis with an account of a patient with functional pulmonary mitral and aortic stenosis, Brit. Heart J 21:325 1959
17. Barlow J B Bosman C. K., Pocock, W A., and Marchand P Late systolic murmurs and non-ejection ("mid late") systolic clicks, Brit. Heart J 30:203 1968.
18. Arevalo, F Meyer E. C. MacCanon, D M and Luisada, A. A. Hemodynamic correlates of the third heart sound Amer J Physiol. 20?:319 1961
19. Dock W., Grandell F and Taubman, F The physiologic third heart sound Its mechanism and relation to protodiastolic gallop, AMER. HEART J 50:449 1955
20. Dayem M K A and Raftery E. B Mechanisms of production of the heart sounds after valve replacement, Amer J Cardiol 18:837 1966.
21. Beck, W Schrire, V and Vogelpoel L. Splitting of the second heart sound in constrictive pericarditis, with observations on the pulsus paradoxus, AMER. HEART J 64:765 1962.

Phillips EM 200 electron microscope. Thick (1 μ) sections of plastic imbedded material were stained with warm crystal violet and examined by light microscopy for orientation and selection of appropriate blocks.

Results

The most conspicuous vascular change consisted of granular deposits within subendothelial and less frequently intramural sites of arterioles which corresponded to arteriolar hyalinization recognizable by light microscopy (Figs. 1A and 1B). Despite the sampling limitation inherent with electron microscopy it appears worthy of note that this lesion was observed in all cases of essential hypertension 66 per cent of those with renal hypertension 71 per cent of those with progressive systemic sclerosis, including both normotensive and hypertensive individuals, 80 per cent of those with gout 75 per cent of the young diabetic patients (Fig. 2) who were all normotensive and 75 per cent of the control subjects (Fig. 3). Arteriolar hyalinosis was encountered in 6 biopsy specimens from patients with essential hypertension with or without superimposed pre-eclampsia. None of the other patients regarded as having toxemia exhibited such vascular change. Further the impression was gained that the lesion was most pronounced in the kidneys of individual with essential hypertension. In the nonischemic kidney of patients with renal hypertension in the cases with progressive systemic sclerosis that exhibited renal failure and hypertension and in the young diabetic patients. On the other hand, the lesion was qualitatively indistinguishable in the various conditions explored. It was comprised of two types of granules (Fig. 4) one of which the more frequently seen was electron-dense and larger in size measuring 100 Å in diameter whereas the other measured 30 to 5 Å. The former granule when examined at

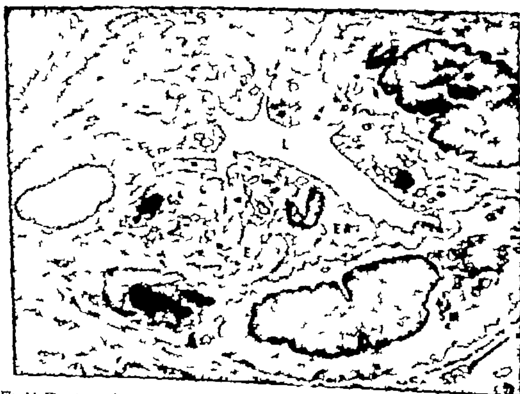


Fig. 1A. Ultrastructural appearance of normal renal arteriole. L = Lumen. En = endothelium. Sm = smooth muscle cell; P = elastica. (×6,300.)

hypertension[1] 4 exhibited a diabetic glucose tolerance test without other stigmata of diabetes and 1 had frank diabetes Renal tissue from both kidneys was available for examination in 4 patients with renal hypertension and from only the ischemic kidney in 2 additional cases[1]

Of the 14 patients with progressive systemic sclerosis[2] 4 exhibited hypertension and 1 died from malignant hypertension and uremic oliguria 24 days after the biopsy

Thirteen patients with classical gouty arthritis were subjected to renal biopsy[3] Although some had previously received uricosuric agents control of their hyperuricemia was considered poor and the drugs had been stopped for at least 3 weeks prior to biopsy Eight of these patients exhibited labile benign hypertension in 4 hypertension was more sustained No consistent relationship between the presence of gout and hypertension was apparent Diminution of renal function as evidenced by decreased glomerular filtration rate elevated blood urea nitrogen and serum creatinine and proteinuria was apparent in the 4 with sustained hypertension

The age range of the 12 patients with juvenile onset diabetes mellitus was from 13 to 23 years.[4] None exhibited vision threatening retinopathy ketoacidosis, or evidence of loss of renal reserves and blood pressure was within the normal range in all cases.

Intravitam percutaneous renal biopsies were performed with a Menghini needle on 51 hypertensive pregnant women Eight were clinically considered as exhibiting moderate pre-eclampsia.[5] Criteria for this diagnosis included consistent blood pressure determinations of 140/90 mm Hg during the last trimester of pregnancy or a rise in blood pressure during this period (30 mm Hg systolic and 15 mm Hg diastolic) Proteinuria exceeding 0 5 Gm per 24 hr was observed in all but 2 of the patients with pre-eclampsia. Edema was variable Eleven patients were classified as severe pre-eclamptics. Elevation of blood pressure occurred within the last trimester of pregnancy and was 160/110 mm Hg or greater Proteinuria exceeding 5 Gm per day and oliguria (400 ml. or less per day) were present consistently Eight patients were considered to have essential hypertension because of elevation of blood pressure throughout the gestational period. Many of these had a previous or family history of hypertension A clinical diagnosis of pre-eclampsia superimposed upon essential hypertension was made on 8 patients. Such patients although hypertensive during the early periods of pregnancy exhibited further rise in blood pressure of at least 30 mm Hg systolic and 15 mm Hg diastolic during the last trimester of pregnancy Proteinuria was noted in 4 A diagnosis of unrelated or primary renal disease was considered in 6 patients. Blood pressure elevation was recognized during the early phase of pregnancy and was associated with massive proteinuria Blood urea nitrogen and serum creatinine levels were elevated in many Ten patients were regarded as exhibiting unclassified toxemia of pregnancy Although elevation of blood pressure occurred usually during the second half of gestation the hypertension was not consistent No previous or familial history of hypertension could be elicited and proteinuria was not encountered

Three patients with severe pre-eclampsia and each with a diagnosis of essential hypertension or primary renal disease exhibited convulsions during the course of their illness

All biopsies were performed within 72 hr following delivery Biopsies were also obtained incidentally during the course of surgery from 4 normotensive patients ranging in age from 50 to 60 years. None exhibited any clinical manifestations of renal disease or diabetes mellitus.

In some instances the biopsy was bisected longitudinally one portion being fixed in either Zenker's acetic or Helly's fluid dehydrated Imbedded in paraffin in the usual manner and stained with hematoxylin and eosin and the periodic acid-Schiff procedure The other portion and in most instances the entire biopsy was cut into 1 mm cubes and fixed in 1 per cent osmium tetroxide buffered with veronal to pH 7 4 dehydrated and imbedded in Maraglas. Ultrathin sections were prepared with a Porter Blum microtome stained with lead citrate and examined with a



Fig. 2. Extensive "hyaline" deposits in wall of renal arteriole from patient with diabetes of juvenile onset. (×6,300.)

lacking the light microscopic appearance of fibrinoid.

Electron-microscopic examination revealed small foci of hyalinosis in vessels that appeared unaltered by light-microscopic examination.

Except in the ischemic kidney of patients with renal hypertension and many of those with toxemia of pregnancy, the juxtaglomerular cells appeared comparable in all cases. The nonspecific granules, indistinguishable from lipofuscin (being comprised of osmophilic cords, clusters, and droplets surrounded by an outer dense peripheral layer) were prominent and secretory granules were infrequent (Fig. 5). The latter were distinguished by a smooth limiting membrane often subtended by a lucent zone containing a matrix of fine granules that occasionally appeared as latticelike arrays. The juxtaglomerular cells of ischemic kidneys from patients with renal hypertension and some with toxemia, on the other hand, were replete with secretory granules and few lipofuscin bodies. The former often exhibited rectangular, pentagonal, trapezoidal, and rhomboidal shapes that were frequently arranged in geometric apposition, particularly in the Golgi zone. Juxtaglomerular cells in such cases also exhibited prominent, dilated endoplasmic reticulum with smooth profiles. Some contained slightly electron-dense material within their confines (Fig. 6).

Cells of the macula densa appeared similar in all the conditions investigated, except that basilar portions of those observed in the ischemic kidneys of patients with renal hypertension appeared to contain more abundant vesicles.

Discussion

Although the most frequent arteriolar change encountered in these biopsies has been aptly designated by light microscopy as hyalinosis, the unequivocal granul

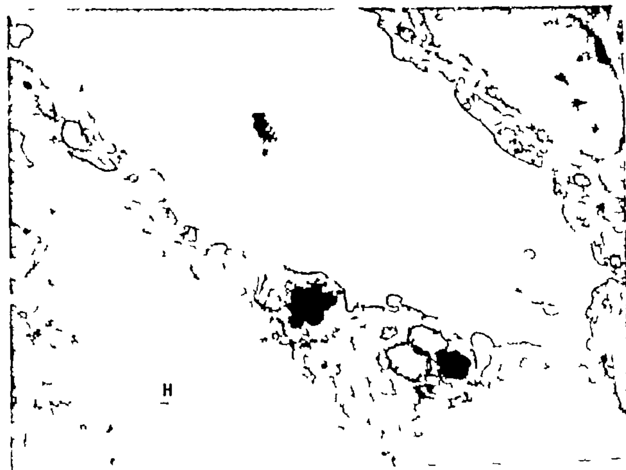


Fig *1B* Portion of renal arteriole from patient with essential hypertension revealing subendothelial deposits of "hyaline" (*H*) (×10 800.)

high magnification exhibited the classical tetrad configuration of ferritin and was morphologically indistinguishable from aliquots of horse ferritin placed directly on Formvar-coated grids and examined at comparable magnifications. When the smaller granules characteristic of arteriolar hyalinosis were compared with grids containing plasma proteins it was noted that they resembled γ (35 Å) and α (35 Å) globulins fibrinogen (35 Å) and hemoglobin (35 Å) in size and density β-globulin and albumin were significantly smaller (approximately 20 Å) Fibrinogen lacked periodic fibers and the β globulin as well as the hemoglobin contained recognizable ferritin particles. Comparable granules measuring 35 to 70 Å in diameter were also noted in in vitro thrombi in addition to banded fibers exhibiting a periodicity of 230 to 240 Å (fibrin) [8]

The subendothelial deposits frequently encroached upon the internal elastic lamina yet in no instance was there incontrovertible evidence that might suggest transitions between this structure and the lesion Similarly no transitions between smooth muscle cells or basement membrane material and the granular deposits could be discerned although these former often exhibited degenerative changes consisting of increased numbers of lipofuscin bodies and mitochondrial vacuolization Endothelial cells exhibited varying degrees of swelling and decreased numbers of organelles. In rare instances endothelial cytoplasm contained granular material indistinguishable from that noted to comprise underlying deposits of so-called hyalinosis.

Fibrinoid degeneration was apparent by light microscopy of thick plastic imbedded tissue in two arterioles from patients with essential hypertension and one with progressive systemic sclerosis. Comparable vessels in ultrathin sections disclosed typical granular deposits as noted in arterioles



Fig. 4 High magnification of "hyaline" deposit revealing its granular nature. T o types of gra ules are p parent. The large ones (circle) often exhibit the tetrad configuration of ferritin. (X180 000.)

may explain the frequent difficulty en countered in determining whether a par ticular vascular lesion exam ned by light microscopy should be designated as fibrinoid or simply hyaline change. Although these findings strongly suggest that so-called hyaline and fibrinoid changes repre sent a spectrum of change rather than distinct entities examination of more sam ples of the latter would appear propitious before final conclusions in this regard are warranted. Recognition of so-called hyalinosis by electron microscopy in vessels that appear normal by light microscopy indi cates that this vascular alteration may be more ubiqu tous than is appreciated

The morphologic evidence relating so-called arteriolar hyalinosis to the deposition of hematogenous components implicates altered vascular permeability in its pathogenesis. Recognition of more pronounced lesions in hypertensive individuals than in normotensive controls is in accord with experimental evidence indicating that hypertension may abet vascular permeabil ity.[24] Whether gout and progressive systemic sclerosis similarly affect vascular permeability is uncertain. It appears more likely to regard the lesions in those in stances as manifestations of hypertension which patients with these disorders fre quently exhibit. Regardless of the mecha nism accounting for the arteriolar lesions in gout and progressive systemic sclerosis, it appears noteworthy that they are qualita tively indistinguishable from those noted in uncomplicated essential hypertension representing further evidence to that previ ously presented[22, 23] militating against the view indicating a singularity of the hyper tension in these diseases.[11, 26] Why such patients exhibit a predilection for the de velopment of essential hypertension remains an enigma although suggestions to account for such an event have been offered.[23] Recognition that arteriolar hyali nosis was also severe in the normotensive adolescent diabetics gives rise to the con

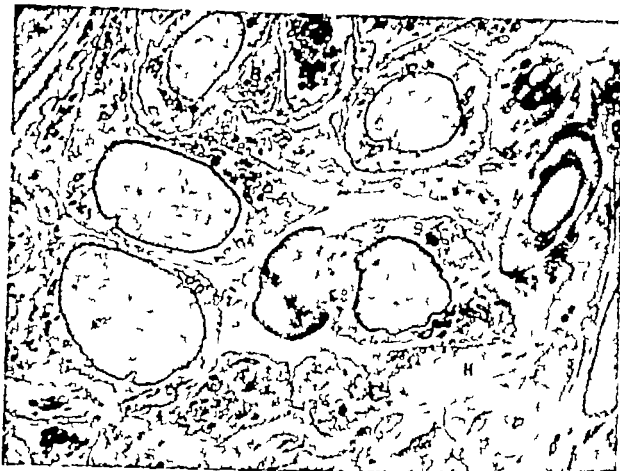


Fig 3 Small focus of "hyal ne" (H) n renal arteriole from normotensive control." (X3 300.)

ultrastructure indicates that this appella tion is erroneous Recognition of the quali tative similarity of so-called hyalinosis in arterioles of normotensive and hyper tensive individuals and the lack of distinguishing features of the deposits in the various disorders explored provides mor phological evidence suggesting a common pathogenesis The lack of convincing evi dence of transitions between the granular deposits and smooth muscle cells, elastica and basement membrane militates against the views, based upon histologic histochemical and other methods, suggesting they derive primarily from these ele ments.[7, 8] On the other hand the identifica tion of ferritin the main storage form of iron particularly when freed by hemor rhage or hemolysis is more consonant with the contention that these deposits are derived hematogenously [7, 11] Recognition of similar granular material within rare endothelial cells and the similarity in size and appearance of the smaller most abundant granular component of the lesion to various plasma proteins in vitro represent addi tional evidence in support of this interpre tation Although fibrin in its classical form was not observed within the lesion it is germane to note that large quantities of granular material morphologically similar to that observed in the arteriolar lesion were present within in vitro thrombi This information therefore does not exclude the presence of fibrinogen and related polymers as a constituent of so-called hyalinosis. Indeed several immunohistochemical studies have disclosed its presence as well as other plasma proteins in some of the arteriolar lesions encountered in the kidneys of hypertensive subjects.[11, 12] It is of interest that the deposits in several ar terioles exhibiting fibrinoid change by light microscopy also lacked fibers possessing the periodicity of fibrin and were ultra structurally indistinguishable from those observed in arterioles lacking a fibrinoid appearance This ultrastructural similarity



Fig 4 Appearance of juxtaglomerular cells from kidney of patient I h toxemia of pregnancy The true secretory granules have assumed paracrystalline forms nd many reside in Gol i lacunae Identical features are observed in ischemic kidney of patients ith renovascular hypertension. (X 20,000)

rise to the possible etiologic role of intra renal arteriolar disease in the pathogenesis of at least some forms of hypertension categorically regarded to be of the essential type.

The impressions obtained concerning the quantitative variations of juxtaglomerular cells and their secretory granules were not surprising and were in accord with the changes n these parameters noted on nu merous occasions in experimental hyper tension[30,31] as well as in man [22,32] This study has revealed striking qualitative differences in juxtaglomerular granules in the various situations explored. Paracrystalline forms were prominent in the ischemic kidneys of patients with renal hypertension and evidence of increased cellular activity notably conspicuous endoplasmic reticulum Golgi structures, and ribosomal RNA particles, characterized the cells harboring such granules. Lipofuscin bodies were sparse in such cells, whereas they were frequent and true secretory granules rare and round or ovoid in the juxtaglomerular cells of the kidneys of normotensive in dividuals as well as those of the hyper tensive patients with gout, progressive systemic sclerosis, and essential hyper tension This appearance of juxtaglomeru lar cells in essential hypertension has also been recently described by Biava and West.[34] Except for the presence of marked vesiculation of basal portions of cells of the macula densa in the juxtaglomerular apparatus of ischemic kidneys from pa tients with renal hypertension, no other abnormalities of this structure were identified that might implicate these cells in renin synthesis or release as was previ ously proposed.[22] Similarly neural elements of the juxtaglomerular apparatus, only infrequently encountered in the specimens studied failed to exhibit alteration or changes that might suggest participation in the formation or release of renin The



Fig 5 Appearance of juxtaglomerular cells from kidney of patient with essential hypertension revealing abundant lipofuscin droplets (*Li*) Only a rare true secretory granule(s) is present. (×12 000.)

sideration that this metabolic disorder may also augment vascular permeability This speculation is compatible with the well recognized predilection of diabetics for the development of arterial and arteriolar disease The information as well as recog nition that qualitatively and often quanti tatively similar vascular lesions may be occasionally encountered by light and electron microscopy in control kidneys of older individuals (over 50 years) provokes some reservation regarding the high incidence of arteriolar hyalinosis in this select group of patients Unfortunately a large number of control specimens from healthy persons of comparable age has not yet become available to us nor are we famil iar with any recorded ultrastructural stud ies providing this information Yet there are certain considerations which prompt us to suggest that this finding was not fortul tous. Although a divergence between light and electron microscopic estimates of ar teriolar hyalinosis in adults has been noted this difference appears relatively small when it is appreciated that comparable vascular lesions are rarely if ever observed by light microscopy in kidneys of children adolescents, or young adults dying from causes unrelated to renal disease. We have failed to detect any significant incidence of arteriolar hyalinosis in the patients with pre-eclampsia uncomplicated by essential hypertension yet they also represent a young population Although objection to the use of data from this group might be raised there is no evidence to indicate that this disorder exerts a protective effect on the renal or other vasculature Indeed the presence of hypertension in these patients might be expected to predispose to such vascular lesions. These considerations not only suggest that there may be common pathogenetic factors in the evolution of the lesions of aging diabetes and hypertension but also further emphasize their close inter relationship The findings in the normotensive adolescent diabetics also again give

tions on the vascular necrosis and renal glomerular lesions of malignant nephrosclerosis, Amer. J. Path. 46:901, 1965.

. Burkholder, P. M.: Malignant nephrosclerosis: an immunohistopathologic study on localized β globulin and fixation of guinea pig complement in human kidneys, Arch. Path. 80:583, 1965.

. Fennell, R. H., Jr., Reddy, C. R. R. M., and Vazquez, J. J.: Progressive systemic sclerosis and malignant hypertension, immunohistochemical study of renal lesions, Arch. Path. 72:209, 1961.

. Esterly, J. A., and Glagov, S.: Altered permeability of the renal artery of the hypertensive rat, an electron microscopic study, Amer. J. Path. 43:619, 1963.

. Fisher, E. R., and Rodnan, G. P.: Pathologic observations concerning the kidney in progressive systemic sclerosis, Arch. Path. 65:29, 1958.

. Bagnall, A. W., and Robinson, H. S.: The development of fatal malignant hypertension in a case of diffuse systemic sclerosis (scleroderma) in the course of treatment with adrenocorticotropin, Clin. Res. Proc. 2:135, 1954.

7. Bartels, E. D., Christensen, L. K., and Ohlsen, A. S.: Renal affection complicating scleroderma, Acta Path. Microbiol. Scand. (Suppl.) 103:174, 1955.

8. Calvert, R. J., and Owen, T. K.: True scleroderma kidney, Lancet 2:19, 1956.

9. Urai, L., Munkacsi, I., and Szinay, G.: New data on the pathology of true scleroderma kidney, Brit. J. Med. 1:713, 1961.

20. Tobian, L., Janecek, J., and Tomboulian, A.: Correlation between granulation of juxtaglomerular cell and extractable renin with experimental hypertension, Proc. Soc. Exp. Biol. Med. 100:91, 1959.

21. Fisher, E. R.: Correlation of juxtaglomerular granulation, pressor activity, and enzymes of macula densa in experimental hypertension, Lab. Invest. 10:707, 1961.

22. Turgeon, C., and Sommers, S. C.: Juxtaglomerular cell count and human hypertension, Amer. J. Path. 38:227, 1959.

23. Boughton, R. M., and Sommers, S. C.: A new concept of renal hypertension, J. Urol. 89:133, 1963.

24. Biava, C. G., and West, M.: Fine morphology of human juxtaglomerular cell in patient with benign essential hypertension, Lab. Invest. 15:1902, 1966.

25. Pollak, V. E., and Nettles, J. B.: The kidney in toxemia of pregnancy: A clinical and pathologic study based on renal biopsies, Medicine 39:469, 1960.

26. Wagener, H. P.: Arterioles of the retina in toxemia of pregnancy, J.A.M.A. 101:1380, 1933.

27. Masson, G. M. C., Corcoran, A. C., and Page, I. H.: Renal and vascular lesions elicited by renin in rats with desoxycorticosterone hypertension, Arch. Path. 53:217, 1952.

similarity in appearance of juxtaglomerular cell granules in several examples of pre-eclampsia in which such structures were available for study to those noted in kidneys from patients with renovascular hypertension might be considered as evidence in support of the possibility that the hypertension of toxemia may be renovascular in origin. Since the subsequent clinical course of such patients militates against the possibility that organic obstructive renovascular disease was present in these instances, the possibility is appealing that the hypertension results from a functional disorder of renal vasculature. In this regard it is of interest to note that vasospasm of retinal arteries has been considered to represent a consistent and helpful diagnostic feature of this form of toxemia.[25,26] Furthermore, a clinical and pathologic syndrome simulating pre-eclampsia may be induced experimentally by the administration of desoxycorticosterone salt and renin.[27] There is considerable evidence identifying the juxtaglomerular cells as the renal source of this latter.

Summary

The ultrastructural appearance of so-called arteriolar hyalinosis was qualitatively indistinguishable in renal biopsies from patients with essential hypertension with or without diabetes mellitus, renovascular hypertension (the unimpaired member), hypertension associated with progressive systemic sclerosis and gout, normotensive aging (greater than 50 years) persons without renal disease, and a high percentage of adolescent normotensive diabetic individuals. These findings provide further evidence identifying the hypertension observed in patients with gout and progressive systemic sclerosis with that of the essential type.

The composition of the lesion of arteriolar hyalinosis strongly suggests its hematogenous derivation rather than primary degenerative nature. The findings also represent morphologic evidence indicating that aging, diabetes, and hypertension may have common pathogenetic factors in their evolution. Recognition of severe arteriolar lesions in adolescent normotensive diabetic patients reaffirms the well-recognized predilection of persons with this disorder to develop vascular disease. It also provokes consideration of a possible role of intrarenal arteriolar hyalinosis in the development of some forms of hypertension.

Study of juxtaglomerular cells by electron microscopy has revealed striking differences in the appearance of their secretory granules in kidneys from patients with essential hypertension and the affected kidney in those whose elevation in blood pressure was attributable to renovascular alteration. The similarity of the granules in patients with pre-eclampsia to those encountered in the latter situation suggests a possible renovascular origin of the hypertension in patients with the toxemia syndrome.

The author gratefully acknowledges the assistance of Dr. Eliseo Perez Stable who performed many of the biopsies. He and Drs. T. S. Danowski, V. Pardo and T. Hayashi provided many of the patients as well as advice.

REFERENCES

1. Fisher, E. R., Perez Stable, E., and Pardo, V.: Ultrastructural studies in hypertension. I. Comparison of renal vascular and juxtaglomerular cell alterations in essential and renal hypertension in man, Lab. Invest. 15:1409, 1966.
2. Pardo, V., Fisher, E. R., Perez-Stable, E., and Rodnan, G. P.: Ultrastructural studies in hypertension. II. Renal changes in progressive systemic sclerosis, Lab. Invest. 15:1434, 1966.
3. Pardo, V., Fisher, E. R., and Perez Stable, E.: Ultrastructural studies in hypertension. III. Gouty nephropathy, Lab. Invest. 18:143, 1968.
4. Fisher, E. R., Perez Stable, E., Amidi, M., Sarver, M. E., and Danowski, T. S.: Ultrastructural renal changes in juvenile diabetics, J.A.M.A. 202:291, 1967.
5. Fisher, E. R., Pardo, V., Paul, R., and Hayashi, T. T.: Ultrastructural studies in hypertension. IV. Toxemia of pregnancy, Amer. J. Path. 55:109, 1969.
6. Hall, C. E.: Electron microscopy of the fibrinogen molecule and the fibrin clot, Lab. Invest. 12:998, 1963.
7. McKinney, B.: The pathogenesis of hyaline arteriolosclerosis, J. Path. Bact. 83:449, 1962.
8. Dugald, J. B., and Anderson, G. S.: The pathogenesis of hyaline arteriolosclerosis, J. Path. Bact. 64:519, 1952.
9. Still, W. J. S., and Hill, K. R.: The pathogenesis of hyaline arteriolar sclerosis, Arch. Path. 68:42, 1959.
10. Blava, C. G., Dyrda, I., Genest, J., and Bencosme, S. A.: Renal hyaline arteriolosclerosis: an electron microscopic study, Amer. J. Path. 44:349, 1964.
11. Paronetto, F.: Immunocytochemical observa-

tions on the vascular necrosis and renal glomerular lesions of malignant nephrosclerosis, Amer. J. Path. 46:901, 1965.

12. Burkholder, P. M.: Malignant nephrosclerosis, an immunohistopathologic study on localized γ-globulin and fixation of guinea pig complement in human kidneys, Arch. Path. 80:583, 1965.
13. Fennell, R. H., Jr., Reddy, C. R. R. M., and Vazquez, J. J.: Progressive systemic sclerosis and malignant hypertension: Immunohistochemical study of renal lesions, Arch. Path. 72:209, 1961.
14. Esterly, J. A., and Glagov, S.: Altered permeability of the renal artery of the hypertensive rat: an electron microscopic study, Amer. J. Path. 43:619, 1963.
15. Fisher, E. R., and Rodnan, G. P.: Pathologic observations concerning the kidney in progressive systemic sclerosis, Arch. Path. 65:29, 1958.
16. Bagnall, A. W., and Robinson, H. S.: The development of fatal 'malignant' hypertension in a case of diffuse systemic sclerosis (scleroderma) in the course of treatment with adrenocorticotropin, Clin. Res. Proc. 2:145, 1954.
17. Bartels, E. D., Christensen, L. K., and Ohlsen, A. S.: Renal affection complicating scleroderma, Acta Path. Microbiol. Scand. (Suppl.) 103:174, 1955.
18. Calvert, R. J., and Owen, T. K.: True scleroderma kidney, Lancet 2:19, 1956.
19. Urai, L., Munkacsi, I., and Szinay, G.: New data on the pathology of true scleroderma kidney, Brit. J. Med. 1:13, 1961.
20. Tobian, L., Janecek, J., and Tomboulian, A.: Correlation between granulation of juxtaglomerular cells and extractable renin with experimental hypertension, Proc. Soc. Exp. Biol. Med. 100:94, 1959.
21. Fisher, E. R.: Correlation of juxtaglomerular granulation, pressor activity and enzymes of macula densa in experimental hypertension, Lab. Invest. 10:707, 1961.
22. Turgeon, C., and Sommers, S. C.: Juxtaglomerular cell counts and human hypertension, Amer. J. Path. 38:227, 1959.
23. Boughton, R. M., and Sommers, S. C.: A new concept of renal hypertension, J. Urol. 89:133, 1963.
24. Biava, C. G., and West, M.: Fine morphology of human juxtaglomerular cells in patients with benign essential hypertension, Lab. Invest. 15:1903, 1966.
25. Pollak, V. E., and Nettles, J. B.: The kidney in toxemia of pregnancy: A clinical and pathologic study based on renal biopsies, Medicine 39:469, 1960.
26. Wagener, H. P.: Arterioles of the retina in toxemia of pregnancy, J.A.M.A. 101:1380, 1933.
27. Masson, G. M. C., Corcoran, A. C., and Page, I. H.: Renal and vascular lesions elicited by renin in rats with desoxycorticosterone hypertension, Arch. Path. 53:217, 1952.

similarity in appearance of juxtaglomerular cell granules in several examples of pre-eclampsia in which such structures were available for study to those noted in kidneys from patients with renovascular hypertension might be considered as evidence in support of the possibility that the hypertension of toxemia may be renovascular in origin. Since the subsequent clinical course of such patients militates against the possibility that organic obstructive renovascular disease was present in these instances, the possibility is appealing that the hypertension results from a functional disorder of renal vasculature. In this regard it is of interest to note that vasospasm of retinal arteries has been considered to represent a consistent and helpful diagnostic feature of this form of toxemia.[25,26] Furthermore, a clinical and pathologic syndrome simulating pre-eclampsia may be induced experimentally by the administration of desoxycorticosterone, salt, and renin.[27] There is considerable evidence identifying the juxtaglomerular cells as the renal source of this latter

Summary

The ultrastructural appearance of so-called arteriolar hyalinosis was qualitatively indistinguishable in renal biopsies from patients with essential hypertension with or without diabetes mellitus, renovascular hypertension (the unimpaired member), hypertension associated with progressive systemic sclerosis and gout, normotensive aging (greater than 50 years) persons without renal disease, and a high percentage of adolescent normotensive diabetic individuals. These findings provide further evidence identifying the hypertension observed in patients with gout and progressive systemic sclerosis with that of the essential type.

The composition of the lesion of arteriolar hyalinosis strongly suggests its hematogenous derivation rather than primary degenerative nature. The findings also represent morphologic evidence indicating that aging, diabetes, and hypertension may have common pathogenetic factors in their evolution. Recognition of severe arteriolar lesions in adolescent normotensive diabetic patients reaffirms the well recognized predilection of persons with this disorder to develop vascular disease. It also provokes consideration of a possible role of intrarenal arteriolar hyalinosis in the development of some forms of hypertension.

Study of juxtaglomerular cells by electron microscopy has revealed striking differences in the appearance of their secretory granules in kidneys from patients with essential hypertension and the affected kidneys in those whose elevation in blood pressure was attributable to renovascular alteration. The similarity of the granules in patients with pre-eclampsia to those encountered in the latter situation suggests a possible renovascular origin of the hypertension in patients with the toxemia syndrome.

The author gratefully acknowledges the assistance of Dr. Eliseo Perez Stable who performed many of the biopsies. He and Drs. T. S. Danowski, V. Pardo, and T. Hayashi provided many of the patients as well as advice.

REFERENCES

1. Fisher, E. R., Perez-Stable, E., and Pardo, V.: Ultrastructural studies in hypertension. I. Comparison of renal vascular and juxtaglomerular cell alterations in essential and renal hypertension in man, Lab. Invest. 15:1409, 1966.
2. Pardo, V., Fisher, E. R., Perez-Stable, E., and Rodnan, G. P.: Ultrastructural studies in hypertension. II. Renal changes in progressive systemic sclerosis, Lab. Invest. 15:1434, 1966.
3. Pardo, V., Fisher, E. R., and Perez-Stable, E.: Ultrastructural studies in hypertension. III. Gouty nephropathy, Lab. Invest. 18:143, 1968.
4. Fisher, E. R., Perez-Stable, E., Amidi, M., Sarver, M. E., and Danowski, T. S.: Ultrastructural renal changes in juvenile diabetics, J.A.M.A. 202:291, 1967.
5. Fisher, E. R., Pardo, V., Paul, R., and Hayashi, T. T.: Ultrastructural studies in hypertension. IV. Toxemia of pregnancy, Amer. J. Path. 55:109, 1969.
6. Hall, C. E.: Electron microscopy of the fibrinogen molecule and the fibrin clot, Lab. Invest. 12:998, 1963.
7. McKinney, B.: The pathogenesis of hyaline arteriolosclerosis, J. Path. Bact. 83:449, 1962.
8. Duguid, J. B., and Anderson, G. S.: The pathogenesis of hyaline arteriolosclerosis, J. Path. Bact. 64:519, 1952.
9. Still, W. J. S., and Hill, K. R.: The pathogenesis of hyaline arteriolar sclerosis, Arch. Path. 68:42, 1959.
10. Blava, C. G., Dyrda, I., Genest, J., and Bencosme, S. A.: Renal hyaline arteriolosclerosis: an electron microscopic study, Amer. J. Path. 44:349, 1964.
11. Paronetto, F.: Immunocytochemical observa-

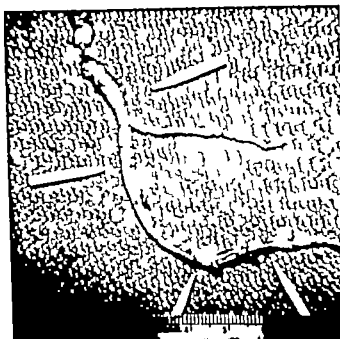


Fig. 1 Right coronary artery cast removed through single proximal arteriotomy Note the acute margl branch at the top of the photograph nd the distal right coronary artery totally thrombosed t the bottom of the photograph.

and atrioventricular branches are removed (Fig 1) Postoperative angiography up to 18 months has proven the effectiveness of this operation in restoring the coronary artery and its branches to complete patency

Background

Endarterectomy has been employed in the peripheral vascular tree for more than a decade. The longevity and sound physiologic nature of the operation is well demonstrated by a ten year follow-up study reported by Cannon and co-workers in January 1970 Exhaustive studies of the biophysical nature of the vascular wall by Sawyer have pointed out the importance of the electronegative surface that normal intima presents to blood. Great concern however over the raw surface left after endarterectomy has caused widespread pessimism as to the possibility that the more positive current of injury would lead to thrombosis of the remaining vessel This has not been the case. Further studies by Sawyer and co-workers have shown that the normal response to endarterectomy is the self limited process of neointima formation which itself presents an electronegative interface to blood. Where acceptable surgical runoff exists, or can be created and where good inflow is established the endarterectomized surface will lay down this neointima with a similar biophysical makeup to the normal intima, and long term patency has been achieved. Exception to this pattern is a group of patients with an essentially metabolic disorder particularly diabetes or inflammatory atherosclerosis, who demonstrate an abnormal healing process in the vascular tree. The usual self limited neointima formation is replaced by a rapid inflammatory response and early reocclusion is seen. This phenomenon has been noted in the peripheral vessels by Wiley and Imperato and in the coronary arteries by Effler Perhaps vein bypass is to be recommended in these situations.

Whereas a vein interposed in the arterial tree presents a highly antithrombogenic, metabolically dynamic intima to confront the blood endarterectomy requires up to

Coronary gas endarterectomy

Martin J Kaplitt M D
George Robinson M D
Bronx N Y

Since the development of selective coronary angiography the direct surgical repair of obstructive coronary disease has attracted widespread interest Direct intervention employing standard endarterectomy and patch graft angioplasty for localized lesions achieved only limited application because of either excessive mortality rates or failure to regularly achieve long term patency of the operated vessels. Consequently these procedures were abandoned in favor of indirect revascularization with internal mammary artery implantation While the implants have been successfully performed and subsequently proved to be functional angiographically a desire to perform successful direct surgery continued to attract experimental and clinical interest. In 1967 the first use of gas endarterectomy in coronary arteries was reported It was felt at that time that certain technical advantages of this new approach would lead to a more favorable and widespread application of the endarterectomy principle in coronary disease A careful analysis of the earlier attempts at mechanical endarterectomy revealed the following important considerations to be responsible for the unsatisfactory results previously obtained

1 Preoperative assessment of the location and extent of coronary lesions was impaired due to the unavailability of suitable coronary radiography
2 Incomplete cleanout of a diffusely diseased vessel occurred
3 Technical difficulties related to closure of the arteriotomy site were present.
4 Failure to reopen side branches ("snow plow" effect) with consequent impaired runoff occurred
5 Application of endarterectomy to the left coronary tree with its attendant high mortality was a factor
6 A lack of appreciation of the ability of the dominant right coronary artery to collateralize the left coronary tree was also responsible

With the problem of accurate coronary angiography solved and having overcome the technical difficulties related to endarterectomy described above gas endarterectomy has now become a part of the surgical armamentarium available to treat obstructive coronary disease In the past three years it has been applied in more than 75 cases in five medical centers in this country Complete removal of disease from a dominant right coronary artery via one or two arteriotomies is readily accomplished Less than 60 min of cardiopulmonary bypass time has been usual Three to 6 inch multibranched casts of the right coronary artery from coronary ostia to posterior descending

From the Department of Surgery Cardiothoracic Division, Montefiore Hospital and Medical Center Bronx, N Y 10467





Fig. 2. Preoperative coronary angiogram with selective injection of right coronary artery. Note the totally occluded right coronary artery just at the origin of the conus branch. A postoperative right coronary injection made two weeks after surgery demonstrates patency of the entire right coronary tree and retrograde filling of the circumflex system from the distal right coronary bed.

diffuse three vessel disease with complete occlusion or diffuse disease of the right coronary artery. Diethrich has reported 40 cases with 5 deaths and 2 late closures. Urschel has performed 20 gas endarterectomies with 3 deaths, 4 early closures, and one late closure.

Discussion

Coronary gas endarterectomy was described in 1967 and shortly thereafter the technique of venous bypass grafting for both left and right coronary arteries was introduced. There followed reports of large numbers of successful bypass cases, and there is little doubt that vein grafts can be constructed for many lesions. Confronted with the problem of the diffusely diseased or totally occluded right coronary artery, however, we are convinced of the superiority of gas endarterectomy. We have utilized the venous bypass principle for

14 days to establish a physiologic neo-intima Patency can be maintained during this period only if certain hemodynamic prerequisites are established at surgery Good inflow must be guaranteed all disease must be removed from the main channel and its side branches and adequate runoff must be assured With these requirements in mind gas endarterectomy was first attempted in more than 300 human cadaver hearts. With the exception of some diabetic and inflammatory type vessels, the vast majority proved to be amenable to this kind of complete reconstruction Studies by Schlesinger detailing the diffuse nature of obstructive coronary disease limited to the main channel and the origin of its side branches, was once again verified Casts removed from the cadaver heart consistently revealed normal intima at the ends of the main channel as well as at the tips of the side branches. This has subsequently been confirmed in the examination of operative specimens. Since the secondary and tertiary branches of the coronary tree are rarely involved with disease the specimen tails off into normal intima in both side and terminal branches.

A final consideration is that angiographic findings consistently lead to an underestimation of the severity of atherosclerotic involvement in any artery Consequently operative situations arise in which arteries considered suitable for vein bypass grafts are found heavily diseased and not ideally suited to this procedure Gas endarterectomy provides an ideal solution to this problem

Several important features of the anatomy and pathology of the right coronary artery are worthy of comment. In 80 to 90 per cent of the population this vessel supplies the posterior surface of the left ventricle through atrioventricular and posterior descending branches, a circumstance defined as the dominant right coronary artery Six named branches of the right coronary artery can collateralize with either the circumflex or anterior descending branches of the left coronary tree. Disease of the right coronary artery is visualized in over 80 per cent of angiographic studies performed for coronary heart disease and in nearly one third of all cases it is the vessel most severely involved by the disease process Additionally it is noteworthy that atherosclerotic lesions in the right coronary artery are usually found further from the coronary ostium than in either the anterior descending or circumflex branches.

Operative technique

With the right atrium and femoral artery cannulated and the patient prepared for partial cardiopulmonary bypass, the right coronary artery is exposed proximal to the acute marginal branch and proximal to the origin of the posterior descending branch Under partial cardiopulmonary bypass, gas endarterectomy is begun by using a 26 gauge needle for introduction of carbon dioxide subadventitially along the full length of the artery and major branches. Either one or two arteriotomies are used to extract the specimen depending upon the ease of extraction Specially designed gas spatulas facilitate removal of the specimen The specimen is carefully examined with respect to length side and terminal branches to verify completeness of the procedure Palpation of the remaining vessel also aids in determining the thoroughness of the cleanout The presence and intensity of backbleeding varies with the degree of preformed intercoronary collaterals and the severity of disease of the left coronary artery Arteriotomy sites are usually closed with a venous patch graft Postoperative anticoagulation has been utilized by some groups.

Results

At the present time more than 75 right coronary gas endarterectomies have been performed (excluding the developmental phase) Robinson has reported on 14 patients 10 of whom have been restudied angiographically Of these 2 were studied over one year postoperatively and demonstrated complete patency The remaining 8 patients were restudied at one month and all but one demonstrated complete patency of the right coronary artery and its side branches. Dramatic retrograde filling of the left coronary tree via the reopened right coronary artery was seen in 5 of these patients (Fig 2) All of the patients operated upon suffered from severe,

Pharmacological blockade of carcinoid flushing provoked by catecholamines and alcohol

Paroxysmal flushing is prominent feature of the carcinoid syndrome. Such flushing is usually but not always, associated ith a rise in the concentration of bradykinin in the blood.[1-4] Bradykinin is formed in the circulating blood by the ction of proteolytic enzyme, kallikrein, produced and released by the carcinoid tumor on plasma kininogen, an alpha-globulin. The primary tumor product is therefore kallikrein, though the active vasodilating substance is bradykinin, and this can be measured in the blood. The paroxysmal nature of carcinoid flushing suggests paroxysmal release of kallikrein, and using plasma bradykinin as an index of kallikrein release, we have investigated the pharmacological mechanisms by which various stimuli, particularly catecholamines nd alcohol, precipitate carcinoid flushing.

When bradykinin (60 μg) was given intravenously as bolus, flushing began in about 40 sec. and lasted about 40 sec. At the height of the flush, the bradykinin concentration in arterial blood rose to levels of between 15 to 120 mμg per milliliter. This procedure mimics, as it ere, the end phase of the carcinoid flush without ny participation by the tumor.

When norepinephrine (6 μg) was given intravenously the expected hyperventilation and facial pallor occurred after 20 sec., hyperventilation lasting about 10 sec. and pallor 15 to 20 sec. Seventy-five seconds after norepinephrine, a flush occurred and was accompanied by rises of arterial blood bradykinin to levels of between 6 to 187 mμg per milliliter. t the peak of flushing. I addition to norepinephrine and epinephrine and certain other catecholamines, intravenous dopamine also provoked flushing, being as potent as norepinephrine but five times less potent (weight for weight) than epinephrine. The time sequence of events in causing flushing was the same for all these catecholamines. These observations suggest that the active catecholamines circulate to the tumor during which time (with norepinephrine and epinephrine) pallor and hyperventilation occur and that the catecholamine then stimulates the release of kallikrein, which elevates the bradykinin content of the blood to flushing levels.

Intravenous phentolamine (3 to 15 mg.) inhibited both the rise in blood bradykinin and the flushing provoked by norepinephrine (6 μg) but did not block either the rise in blood bradykinin or the flush caused by directly administered bradykinin, doses producing the same degree of flushing. effects of norepinephrine and dopamine were m easily blocked (15 mg. of phentolamine) tha w those of epinephrine (60 mg.).

It would seem that the catecholamines timul the tumor cell t release kallikrein nd that receptor site or sites on the tumor cell which sensitive to catecholamines are blocked by phent amine. Phenoxybenzamine, another predominan lpha-adrenergic blocking agent, also inhibit norepinephrine-induced flushing, while the be adrenergic blocking gent, propranolol, was ineff tive.[5,6] The correlation between the blockade flushing and rises of blood bradykinin is further direct evidence that *bradykinin is the agent respo sible for flushing in these circumstances.*

In 5 out of 12 patients with the carcinoid sy drome, flushing was provoked by ethanol. Or ethanol (4 ml. of 95 per cent ethanol) and intr venous ethanol (10 ml. of 4.75 per cent solutio provoked flushing which, in contrast to bradykini and catecholamine-induced flushing, did not beg until 130 to 150 sec. after administration. Ethano induced flushing was also accompanied by a rise blood bradykinin.

Not all patients respond to ethanol, and som who do respond are unresponsive to a further do given few minutes after the first, and requir several hours to recover their responsiveness. Unre sponsiveness to the administration of ethanol not associated with rise in blood bradykinin However during these periods of unresponsivenes to ethanol, these patients till respond to catechol amines. In two cases, alcohol-induced flushing wa blocked ith large doses of intravenous phentola mine (40 to 70 mg.) similar to the doses required t block epinephrine-induced flushing.

How can these effects of alcohol be explained? The timing of events is compatible either with alcohol acting directly but slowly on the tumor to release kallikrein, or with alcohol releasing an inter mediary substance which secondarily releases tumor kallikrein. *If* alcohol is acting directly on the tumor certain effects must be explained. First, there is definite delay in the onset of the alcohol-induced flush. This is not due to the time taken for oral alcohol to be absorbed, since the delay is the same for intravenous alcohol and Mendelson[7] has shown

localized proximal and mid coronary occlusions and applied gas endarterectomy to the diffusely diseased vessel

The dominant right coronary artery has the potential for extensive collateral blood supply to the branches of the left coronary system as shown by our early postoperative radiographic studies. Some of these collateral sources arise in the diseased segment of the artery that would have been bypassed by a long vein graft inserted into the distal right coronary artery Short term patency was demonstrated in 8 cases and long term patency was found in 2 at 12 and 14 months. There have been no late closures in our patients who were restudied

To what extent the right coronary artery is ultimately capable of revascularizing the heart is unknown at this time In this group of patients there were five instances where at early postoperative restudy the reopened dominant right coronary artery perfused an extensive mass of left ventricular myocardium suggesting that it may be capable of perfusing the entire heart as progressive disease takes place in the left coronary tree

Conclusion

Coronary gas endarterectomy has now been utilized clinically in more than 75 cases and both early and late angiographic follow up suggest that this operation having overcome many of the problems associated with mechanical endarterectomy can now assume its proper role in the surgical treatment of diffuse coronary artery disease

REFERENCES

1 Sawyer P N Kaplitt M J Sobel S, et al. Experimental and clinical experience with coronary gas endarterectomy Arch. Surg (Chicago) 95:736 1967
2 Pilcher D B Barker W F., and Cannon, J A. An aortoiliac endarterectomy case series followed 10 years or more Surgery 67:5, 1970.
3 Sawyer P N., Zuhdi D Wesolowski, S. A., et al Electrical surface charge as a factor in maintenance of patency of endarterectomized aorta Surgery 59:1019 1966.
4 Sawyer P N Biophysical mechanisms in vascular homeostasis and intravascular thrombosis, New York 1965 Appleton-Century-Crofts, Inc.
5 Imperato, A. J Analysis of failure of arterial reconstruction J Cardiovasc. Surg 57:227 1969 (Special issue.)
6. Robinson, G. Kaplitt, M J., Philips, P and Patel B Complete surgical correction of the totally occluded and diffusely diseased right coronary artery J Thorac. Cardiovasc. Surg. (In press.)
7 Diethrich, E. B Personal communication.
8 Urschel, H C. Personal communication.

as soft and scaphoid there was no hepatosplenomegaly. A nontender pulsatile mass approximately 8 cm. in diameter was palpable in the left lower quadrant. Pulsations could be felt cephalad to the mass but not below it. The femoral and dorsalis pedis pulses, however, were palpable bilaterally.

A retrograde aortic catheterization with angiography was performed via a left brachial arteriotomy. The aortic pressure was 178/72 mm. Hg. The aortogram revealed diffusely atherosclerotic and tortuous abdominal aorta with no aneurysm. After the catheter was withdrawn, the artery distal to the arteriotomy was flushed with heparin, and the incision was subsequently closed with interrupted No. 6-0 Tevdek. The skin was closed with mattress sutures using No. 3-0 silk. The radial pulse was 3 plus on a scale of 4. There was no active blood leakage 24 hours after catheterization.

Two months following discharge, he was readmitted because of coldness of the left hand, "buzzing" sensation in the left elbow, and sensation of fatigue in the left arm following manual exertion. The general physical examination findings were unchanged except for a continuous murmur and thrill in the left antecubital area at the site of recent cut-down. Branham's sign (slowing of the pulse with manual compression of the fistula) was not demonstrable. The left radial pulse was 2 plus on a scale of 4.

At surgery, an aneurysmal sac of the left brachial artery was found communicating with the median basilic vein. The arteriovenous fistula was surgically obliterated by division and the artery and vein were repaired.

Several factors probably contributed to the arteriovenous fistula formation. The poorly retracting sclerotic brachial artery leaked blood through the repaired arteriotomy site, permitting formation of a pulsating hematoma. Propelled and enlarged by the high arterial pressure, the pulsating hematoma followed a course of least resistance (through the cutdown) outward to the subcutaneous tissue. Erosion of the median basilic vein occurred probably because of the stress of the hematoma was directed upward from the artery. This is also probably why the brachial vein accompanying the artery was spared.

The unusual occurrence of an arteriovenous fistula following arteriotomy is presented to stress that potentially life-threatening complications[1-10] could result from a seemingly simple procedure. It is further stressed that care must be exercised and excessive trauma to large vessels should be avoided, especially in hypertensive patients with atherosclerotic vessels to prevent similar complications.

Lamberto C. Marumba, M.D.
Roger P. Javier, M.D.
Frank J. Hildner, M.D.
Philip Samet, M.D.
Division of Cardiology
Department of Internal Medicine
Mount Sinai Hospital
Miami Beach, Fla.

Present Address: Beckley Medical Arts, Inc., 101 S. Kanawha, Beckley, W. Va.

REFERENCES

1. Zimmerman, H. A., Scott, R. W., and Becker, N. O.: Catheterization of left side of the heart in man, Circulation 1:357, 1950.
2. Ross, R. S.: Arterial complications in cooperative study on cardiac catheterization, Braunwald, E., and Swan, H. J. C., editors, Circulation 37(Suppl. 3):39, 1968.
3. Voci, G., and Hamer, N. A. J.: Retrograde arterial catheterization of the left ventricle, Amer. J. Cardiol. 5:493, 1960.
4. Hildner, F. J., Drake, F. H., Gale, H. H., and Ormond, R. S.: Transbrachial retrograde left heart catheterization: Evaluation of 600 consecutive cases in adults, Amer. J. Cardiol. 18:52, 1966.
5. Vlad, P., Joh, A., and Lambert, E. C.: Retrograde arterial catheterization of the left heart, Circulation 29:787, 1964.
6. Ross, R. S.: Personal communication.
7. Shumacker, H. B., Jr., and Wayson, E. E.: Spontaneous cure of aneurysms and arteriovenous fistulas, with some notes on intravascular thrombosis, Amer. J. Surg. 79:532, 1950.
8. Elkin, D. C., and Warren, J. V.: Arteriovenous fistulas: Their effect on the circulation, J.A.M.A. 134:1524, 1947.
9. Dorney, E. R.: Peripheral A-V fistula of fifty-seven years duration with refractory heart failure, Amer. Heart J. 54:778, 1957.
10. Burchell, H. B.: Unusual causes of heart failure, Circulation 21:436, 1960.

The rocker

Patients inquire regularly about exercise. The type, degree, and rate of physical exertion must fit the state of health of each patient. The feeble, old, or invalid patient usually needs some exercise to maintain a satisfactory state of health. The old patient is particularly in need of exercise even in the absence

that alcohol is present in the systemic circulation within two minutes of an oral dose and presumably earlier in the portal circulation bathing hepatic carcinoid metastases. Second, some patients become unrespon ive to alcohol while retaining their responsiveness to catecholamines, indicating that the tumor still contains kallikrein and that the flushing system is till intact. Third, alcohol-induced flushing can be blocked by alpha adrenergic blocking agents.

We suggest that these phenomena can best be interpreted by assuming that alcohol releases a catecholamine from certain tissue stores and that this catecholamine then circulated to the tumor to release kallikrein. There are precedents for the release of catecholamines from ti sue stores.[12, 13] Thi hypothesis would explain the time lag in alcohol induced flushing on the ba is of time taken to release the catecholamine and then its circulation to the tumor cell and also the blocking of alcohol induced flushing by alpha adrenergic blocking agents, by blocking the action of thi proposed catecholamine mediator on the tumor cell. We believe such a mediator i not epinephrine norepinephrine nor dopa mine and that a caref il examinat on of ga trointestinal mucosa for other catecholamine as a mediator of carci oid flushi g i warr nted

A. R. Adamson
D. G. Grahame Smith
W. S. Peart
M. Starr
Medical Un t nd Department of Pharmacology
St M ry s Hospital Medical School
London W 2 England

REFERENCES

1. Oates, J. A., Melm n, K., Sjoerdsma, A., Gillespie, L., and M son, D. T.: Release of a kinin peptide in the carcinoid syndrome, Lancet 1:514, 1964.
2. Oates, J. A., Pettinger, W. A., and Doctor, R. B.: Evidence for the release of bradykinin in carcinoid syndrome, J. Clin. Invest. 45:173, 1966.
3. Oates, J. A., and Melmon, K.: In Erdos, E. G., Bach, N., and Sicuteri, F., editors: International symposium on hypotensive peptides, held in Florence, 1965, New York, 1966, Springer Verlag, p. 565.
4. Webster, M. E.: In Erdos, E. G., Bach, N., and Sicuteri, F., editors: International symposium on hypotensive peptides, held in Florence, 1965, New York, 1966, Springer Verlag, p. 263.
5. Zeitlin, I. J.: In Erdos, E. G., Bach, N., and Sicuteri, F., editors: International symposium on hypotensive peptides, held in Florence, 1965, New York, 1966, Springer Verlag, p. 576.
6. Zeitlin, I. J., and Smith, A. N.: 5-hydroxyindoles and kinins in the Carcinoid and Dumping Syndromes, Lancet 2:986, 1966.
7. Allwood, M. J., and Lewis, G. P.: Bradykinin and forearm blood flow, J. Physiol. (London) 170:571, 1964.
8. Adamson, A. R., Grahame-Smith, D. G., Peart, W. S., and Starr, M.: Pharmacological blockade of carcinoid flushing provoked by catecholamines and alcohol, Lancet 2:293, 1969.
9. Levine, R. J., and Sjoerdsma, A.: Pressor amines and the carcinoid flush, Ann. Intern. Med. 58:818, 1963.
10. Oates, J. A., and Butler, T. C.: Pharmacologic and endocrine aspects of carcinoid syndrome, Advances Pharmacol. 5:109, 1967.
11. Mendelson, J. H.: Ethanol 1-C14 metabolism in alcoholics and nonalcoholics, Science 159:319, 1968.
12. Perman, E. S.: The effect of ethyl alcohol on the secretion from the adrenal med lla of the cat, Acta Physiol. Scand. 48:323, 1960.
13. Abelin, I., Herren, C., and Berli, W.: Über die Rolle des Adrenalins, Noradrenalins und Oxytyramin bei der spezifischdynamischen Wirkung des Eiweisses und der Aminosäuren, Helv. Med. Acta 25:591, 1958.

Arteriovenous fistula complicating brachial arteriotomy

Brachial arteriotomy has gained wide use in cardiac catheterization procedures. There are many reports of arterial cutdown complications to date,[1-4] but arteriovenous fistula formation following repaired arteriotomy has not yet been described. In a recent study which involved 7,311 retrograde catheterizations utilizing both percutaneous and arterial cutdown techniques, two patients developed peripheral arteriovenous fistula involving in both cases, the right femoral vein and artery.[3,4] In both instances, entry to these vessels was gained percutaneously. We would like to describe a similar complication following arteriotomy.

The patient was a 77 year-old Caucasian woman referred for evaluation of a pulsating abdominal mass suspected to be an abdominal aortic aneurysm. The blood pressure was 170/80 mm. Hg. Pertinent findings were limited to the abdomen. The abdomen

was soft and scaphoid; there was no hepatosplenomegaly. A nontender pulsatile mass approximately 8 cm. in diameter was palpable in the left lower quadrant. Pulsations could be felt cephalad to the mass but not below it. The femoral and dorsalis pedis pulses, however, were palpable bilaterally.

A retrograde aortic catheterization with angiography was performed via a left brachial arteriotomy. The aortic pressure was 178/72 mm. Hg. The aortogram revealed a diffusely atherosclerotic and tortuous abdominal aorta with no aneurysm. After the catheter was withdrawn, the artery distal to the arteriotomy was flushed with heparin, and the incision was subsequently closed with interrupted No. 6-0 Tevdek. The skin was closed with mattress sutures using No. 3-0 silk. The radial pulse was 3 plus on a scale of 4. There was no active blood leakage 24 hours after catheterization.

Two months following discharge she was readmitted because of coldness of the left hand, a "buzzing" sensation in the left elbow, and sensation of fatigue in the left arm following manual exertion. The general physical examination findings were unchanged except for a continuous murmur and thrill in the left antecubital area at the site of recent cut-down. Branham's sign (slowing of the pulse with manual compression of the fistula) was not demonstrable. The left radial pulse was 2 plus on a scale of 4.

At surgery, an aneurysmal sac of the left brachial artery was found communicating with the median basilic vein. The arteriovenous fistula was surgically obliterated by division and the artery and vein were repaired.

Several factors probably contributed to the arteriovenous fistula formation. The poorly retracting sclerotic brachial artery leaked blood through the repaired arteriotomy site, permitting formation of a pulsating hematoma. Propelled and enlarged by the high arterial pressure, the pulsating hematoma followed a course of least resistance (through the cutdown) outward to the subcutaneous tissue. Erosion of the median basilic vein occurred probably because of the stress of the hematoma was directed upward from the artery. This is also probably why the brachial vein accompanying the artery was spared.

The unusual occurrence of an arteriovenous fistula following arteriotomy is presented to stress that potentially life-threatening complications[1-10] could result from a seemingly simple procedure. It is further stressed that care must be exercised and excessive trauma to large vessels should be avoided, especially in hypertensive patients with atherosclerotic vessels, to prevent similar complications.

Lamberto C. Marambo, M.D.
Roger P. Jeruer, M.D.
Frank J. Hildner, M.D.
Philip Samet, M.D.
Division of Cardiology
Department of Internal Medicine
Mount Sinai Hospital
Miami Beach, Fla.

Present Address: Beckley Medical Arts, Inc., 2101 S. Kanawha, Beckley, W. Va.

REFERENCES

1. Zimmerman, H. A., Scott, R. W., and Becker, N. O.: Catheterization of left side of the heart in man, Circulation 1:357, 1950.
2. Ross, R. S.: Arterial complications in cooperative study on cardiac catheterization, Braunwald, E., and Swan, J. J. C., editors, Circulation 37(Suppl. 3):39, 1968.
3. Voci, C., and Hamer, N. A. J.: Retrograde arterial catheterization of the left ventricle, Amer. J. Cardiol. 5:493, 1960.
4. Hildner, F. J., Drake, E. H., Gale, H. H., and Ormond, R. S.: Transbrachial retrograde left heart catheterization. Evaluation of 600 consecutive cases in adults, Amer. J. Cardiol. 18:52, 1966.
5. Vlad, P., Jok, A., and Lambert, E. C.: Retrograde arterial catheterization of the left heart, Circulation 29:787, 1961.
6. Ross, R. S.: Personal communication.
7. Shumacker, H. B., Jr., and Wayson, E. E.: Spontaneous cure of aneurysms and arteriovenous fistulas, with some notes on intravascular thrombosis, Amer. J. Surg. 79:532, 1950.
8. Elkin, D. C., and Warren, J. V.: Arterio-venous fistulas: Their effect on the circulation, J.A.M.A. 134:1524, 1947.
9. Dorsey, E. R.: Peripheral A-V fistula of fifty-seven years duration with refractory heart failure, Amer. Heart J. 84:778, 1957.
10. Burchell, H. B.: Unusual causes of heart failure, Circulation 21:436, 1960.

The rocker

Patients inquire regularly about exercise. The type, degree, and rate of physical exertion must fit the state of health of each patient. The feeble, old, or invalid patient usually needs some exercise to maintain a satisfactory state of health. The old patient is particularly in need of exercise even in the absence

that alcohol is present in the systemic circulation within two minutes of an oral dose and presumably earlier in the portal circulation bathing hepatic carcinoid metastases. Second some patients become unrespon ive to alcohol while retaining their responsiveness to catecholamines, indicating that the tumor still contains kallikrein and that the flushing system is still intact. Third, alcohol induced flushing can be blocked by alpha adrenergic blocking agents.

We suggest that these phenomena can best be interpreted by assuming that alcohol releases a catecholamine from certain ti sue stores and that this catecholamine then circulated to the tumor to release kallikrein. There are precedents for the release of catecholamines from ti sue stores.[12,13] Thi hypothesis would explain the time lag in alcohol induced flu hing on the basi of time taken to release the catecholamine and then its circulation to the tumor cell and also the blocking of alcohol-induced flushing by alpha adrenergic blocking agent by block ng the action of this proposed catecholamine mediator on the tumor cell. We believe such a medi ator i not epinephrine norepinephrine nor dopa mine and that a careful examination of ga trointestinal mucosa for another catecholamine a a mediator of carcinoid flu h ng is warr nted

I R *Adamson*
D G Grahame Smith
W S Peart
M Starr
Medical U t and Department of Pharmacology
St M ry s Hospital Med cal School
London W 2 Engla d

REFERENCES

1 Oates, J A Melmon, K. Sjoerd ma A. Cil lespie L. and Mason D T Release of a kinin peptide in the carcinoid syndrome Lancet 1:514 1964
2 Oates, J A. Pettinger W A. and Doctor R. B Evidence for the release of bradykini in carcinoid syndrome J Clin. Invest. 45:173 1966.
3 Oates, J A. and Melmon, K.: *In* Erdos, E. G Bach N., and Sicuteri, F editors. International symposium on hypotensive peptides, held in Florence 1965 New York, 1966, Springer Verlag p. 565
4 Webster M E. *In* Erdos, E. G., Bach, N and Sicuteri F., editors. International symposium on hypotensive peptides, held in Florence, 1965, New York 1966 Springer Verlag p. 263.
5 Zeitlin, I J *In* Erdos, E. G Bach, N and Sicuteri, F., ed tors International symposium on hypotensive peptides, held in Florence, 1965, New York, 1966, Springer Verlag p. 576.
6. Zeitlin I J and Smith, A. N 5-hydroxyindoles and kinin in the Carcinoid and Dumping Syndromes Lancet 2:986 1966.
7 Allwood M J and Lewis, G. P Bradykinin and forearm blood flow J Physiol. (London) 170:571 1964
8. Adamson A R. Grahame-Smith D C Peart, W S., and Starr M Pharmacological blockade of carcinoid flushing provoked by catechol mines and alcohol Lancet 2:293, 1969
9 Levine R. J and Sjoerdsma A. Pressor amines and the carcinoid flush A n. Intern. Med 58:818 1963
10 Oates, J A. and Butler T C. Pharmacologic and endocrine aspect of carcinoid syndrome, Advances Pharmacol. 5:109 1967
11 Mendelson J H Ethanol-1 C14 metabolism alcoholics and nonalcoholics, Science 159:319 1968.
12. Perman, E. S The effect of ethyl alcohol on the secretion from the adrenal medulla of the cat Acta Physiol. Scand. 48:323 1960.
13 Abelin, I Herren C. and Berl W Über die Rolle des Adrenalins, Noradrenal ns und Oxytyramin bei der spezifischdynamischen Wirkung des Eiweisses und der Aminosä ren, Helv Med Acta 25:591 1958.

Arteriovenous fistula complicating brachial arteriotomy

Brachial arteriotomy has gained wide use cardiac catheterization procedures. There are many reports of arterial cutdown complications to date,[1-4] but arteriovenous fistula formation following repaired arteriotomy has not yet been described. In a recent study which involved 7 311 retrograde catheterizations utilizing both percutaneous and arterial cut down techniques, two patients developed peripheral arteriovenous fistula involving in both cases, the right femoral vei and artery.[5] In both instances entry to these vessels was gained percutaneously We would like to describe similar complication following arteri tomy

The patient was a 77 year-old Caucasian woman referred for evaluation of a pulsating abdominal mass suspected to be an abdominal aortic aneurysm. The blood pressure was 170/80 mm Hg Pertinent findings were limited to the abdomen. The abdomen

as soft and scaphoid there as no hepatosplenomegaly A nontender pulsatile mass pproximately 8 cm. in diameter was palpable in the left lower quadrant. Pulsations could be felt cephalad t the mass but not below it. The femoral nd dorsalis pedis pulses, however were palpable bilaterally

A retrograde aortic catheterization with angiography as performed via left brachial arteriotomy The aortic pressure was 178/72 mm. Hg The aortogram revealed diffusely atherosclerotic and tortuous abdominal aorta with no aneurysm. After the catheter was ithdrawn, the artery distal t the arteriotomy was flushed ith heparin, nd the incision as subsequently closed with interrupted No. 6-0 Tevdek. The skin was closed with mattress sutures using No. 3-0 silk. The radial pulse wa 3 plus on a scale of 4. There was no active blood leakage 24 hours after catheterization.

T months following discharge she as readmitted because of coldness of the left hand, "buzzing sensation in the left elbow and sensation of fatigue in the left arm following manual exertion. The general physical examination findings were unchanged except for continuous murmur and thrill in the left ntecubital area t the site of recent cut down. Bra ham sign (slowing of the pulse ith manual compression of the fistula) as not demonstrable The left radial pulse was 3 plus on scale of 4.

At surgery an neurysmal sac of the left brachial artery as found communicating th the median basilic ein. The arteriovenous fistula as surgically obliterated by division nd the artery and ves ere repaired.

Several factors probably contributed t the arteriovenous fistula formation. The poorly retracting sclerotic brachial artery leaked blood through the repaired arteriotomy site, permitting formation of a pulsating hematoma. Propelled and enlarged by the high arterial pressure, the pulsating hematoma followed course of least resistance (through the cutdow) outward to the subcutaneous tissue. Erosion of the median basilic vein occurred probably because of the stress of the hematoma as directed upward from the artery. This is also probably why the brachial vein accompanying the artery was spared.

The unusual occurrence of an arteriovenous fistula following arteriotomy is presented to stress that potentially life-threatening complications[1-10] could result from seemingly simple procedure. It is further stressed that care must be exercised and excessive trauma to large vessels hould be avoided especially in hypertensive patients with therosclerotic vessels to prevent similar complications.

Lamberto C. Maramba M.D
Roger F Jeter M.D
Fra k J Hildner M.D
Philip Samet, M.D
Division of Cardiology
Department of Internal Medicine
Mount S ai Hospital
Miami Beach Fla

Present Address: Beckley Medical Arts, Inc 2401 S. Kana ha, Beckley W Va.

REFERENCES

1 Zimmerman, H A. Scott, R. W nd Becker N O Catheterization of left sid of the heart in man, Circulation 1:357 1950.
2. Ross, R S Arterial complication In cooperative study on cardiac catheterization, Braunw ld E C nd Swan, J J C., ed tors Circulation 37(Suppl. 3):39 1968.
3. Lord, G., nd Hamer N A J Retrograde arterial catheterization of the left ventricle Amer J Cardiol. 5 493 1960
4. Hildner F J Drake P H Gale H H nd Ormond, R S. Transbrachial retrograde left heart catheterization Eval ation of 600 consecutive cases in adults, Amer J Cardiol. 18:32 1966.
5 Vlad, P Job A., and Lambert, E C Retrograde arterial catheterization of the left heart, Circulation 29 787 1964.
6. Ross, R. S. Personal communication.
7 Shumacker H. B J and W yam, C. C. Spontaneous cure of neurysms and arteriovenous fistulas, with some notes on intravascular thrombosis, Amer J Surg. 79:532, 1950.
8. Elkin, D C., and Warren, J V Arterio-venous fistula Their effect on the circulation J A.M.A. 134 1524, 1947
9 Dorney E. R. Peripheral A V fistula of fifty seven years duration ith refractory heart failure, Amer. Heart J 54 778, 1957
10 Burchell H. B. Unusual causes of heart failure Circulation 21:436, 1960.

The rocker

Patients inquire regularly about exercise. The type, degree, and rate of physical exertion must fit the state of health of each patient. The feeble, old, or invalid patient usually needs some exercise to maintain satisfactory state of health. The old patient is particularly in need of exercise even in the absence

of illness. Gentle but definite exercise is especially good for the old patient as well as for the recuperating feeble one The rocker affords good exercise even while the patient sits relaxed It is safe for the weak and feeble All of the muscles of the body participate in gentle rocking The joints, viscera, and other parts of the body move constantly Rocking is pleasant, soothing and gentle. Recall how the fretful, crying child is quieted and even falls asleep when rocked Rocking is conducive to pleasant and relaxing conversation. People do not tend to argue or become unduly excited while peacefully rocking The same soothing exercise applies to the glider and old fashion porch swing The physician should keep the rocker in mind as an excellent means of exercise for old feeble, or ill patients. More rockers are needed in homes—large, comfortable, and relaxing rockers. Hospitals, clinics and nursing homes all need rockers—a rarity in American hospitals except for our ward at the Charity Hospital.

G E Burch, M.D
T D Giles, M.D.
H L. Colcolough, M.D
Department of Medicine
Tulane University School of Medicine
New Orleans, La.

Antilymphocyte serum blockade of the reticuloendothelial system

Antilymphocyte serum (ALS) has been used as an immunosuppressive agent in human organ transplantation. It probably affects the immune response in a number of ways. One of the suggested mechanisms is to produce a reduction in the number of stimulated antigen-sensitive or reactive cells.[1]

To elucidate what effect ALS might have on the fixed phagocytic cells of the reticuloendothelial system (RES) we have studied the blood clearance of colloidal particles in mice pretreated with ALS.[2] Administration of ALS caused profound impairment in the clearance of the two tested colloids, aggregated human serum albumin (AA) and carbon. ALS administered by intravenous injection produced the most marked impairment, and when AA was used as the test colloid, blockade was immediate but transient. In contrast, impaired clearance of colloidal carbon was demonstrable up to four days following a single intravenous injection.

Studies to clarify the mechanisms by which ALS produces its RES-blockading effect are presently in progress. It appears that its action may be much more complex than our initial studies indicated and that the two colloids may be affected in different ways.

Other investigators have also reported alterations in RES phagocytosis after administration of antimacrophage or ALS. Impaired carbon clearance has been described in guinea pigs[4] and rats[5] treated with either ALS or antimacrophage serum. The relationship, if any between the RES-blockading activity of ALS and its immunosuppressive properties is still not clear although antimacrophage sera, which do produce blockade, seem to lack the immunosuppressive properties of ALS.[3]

Whether or not alteration in RES phagocytosis occurs in humans given ALS remains to be demonstrated If it does, it is intriguing to speculate on the ramifications of that possibility For example, might ALS be useful in prolonging the blood levels of certain drugs which are administered in particulate form (such as Amphotericin B) or which depend on RES cells for their clearance? In fact, might these factors help explain the well-known potentiation of other immunosuppressive drugs by ALS?[4] Similarly might ALS be of use in decreasing the rate of uptake and destruction of formed elements of the blood as occurs in hemolytic anemias, incompatible blood transfusions, and autoimmune platelet and white blood cell disorders? These provocative clinical questions await further investigation.

John N Sheagren, M.D
Joseph B Edelin
Laboratory of Clinical Investigation
National Institute of Allergy and Infectious Diseases
Rolf F Barth, M.D
Richard A Malmgren M.D
Pathologic Anatomy Branch
National Cancer Institute
Bethesda Md. 20014

REFERENCES

1. Kashiwagi, N., Brantigan, C. O Brettschneider L., Groth C. G. and Starzl T E. Clinical reactions and serologic changes after the administration of heterologous antilymphocyte globulin to human recipients of renal homografts. Ann. Intern. Med. 68 275 1968.
2. Barth R. F Studies on heterologous anti-

lymphocyte and antithymocyte sera. IV. Further evidence for a preferential effect on antigen-sensitive cells, J. Immunol. 103:648, 1969.
3. Sheagren, J. N., Barth, R. F., Edelin, J. B., and Malmgren, R. A.: Reticuloendothelial blockade produced by antilymphocyte serum, Lancet 2:297, 1969.
4. Loewi, G., Temple, A., Nind, A. P. P., and Axelrad, M.: A study of the effects of antimacrophage sera, Immunology 16:99, 1969.
5. Grogan, J. B.: Alterations in phagocytic function of rats after treatment with antilymphocyte serum, J. Reticuloendothel. Soc. 6:111, 1969.
6. Russell, P. S.: Antilymphocyte serum as an immunosuppressive agent, Ann. Intern. Med. 68:483, 1968.

Letters to the editor

Left atrial rhythm

To the Editor

Left atrial rhythm Vectorcardiographic study and electrophysiologic critical evaluation by Piccolo and associates[1] is a nice analysis of the problem. I would only object that, despite their better theoretic basis, vectorcardiogram (VCG) lead systems are no more conclusive than the electrocardiogram (ECG) in determining the precise location of a pacemaker However the authors have properly placed their data in the context of the relevant literature and thus upport the conclusions of Massumi and Tawakkol's outstanding original studies In 1961 we published what appeared to be the fir t ECG series reporting the variable vector orie tation of atrial activ ation in the horizontal plane in associati w th inverted P_{II} P_{III} and aV_F during coronary inus rhythm [3] The experimental literature even at that time permitted no fixed conclusions to the site of the pacem ker The results n ll these report [4] illustrate the haz ards of excessive ext apolation in electrocardiog raphy exemplified by certain tudies on left atrial rhythm

Arrhythmia analysis h lways nvited the con struction of great i erted pyramids in which a mass of explication must rest on one or two shaky assumptions. This has bee an irresistible attr iction for ntellectual gamesmanship which in fairness, often does provide worthwhile me t l cali thenics to at least sharpen our approach to the ECG How ever in considering this kind of study one mu t keep in mind that all the resulting deductive terpretations remain in limbo, subject to def nitive investigation, i.e., studies done directly on the heart nd if possible, in human beings. In the case of left atrial (LA) rhythm this has been done by Mass mi and supported by Piccolo and co-workers who have avoided the trap of excessive intellectualization of the overworked electrocardiogram.

David Spodick M.D
Tufts University School of Medicine
Department of Medici e
Lemuel Shattuck Hospital
Boston Mass.

REFERENCES

1. Piccolo, E., Nava, Andrea, Furlanello, Francesco, Pernutti, Bruno and Dalla Volta, Sergio Left atrial rhythm. Vectorcardiographic study and electrophysiologic critical evaluation, Amer. HEART J 80:11 1970.
2. Massumi R. and Tawakkol A. A. Direct study of left atrial P waves, Amer J Cardiol. 20:331 1967
3. Spodick, D H and Colman, R. Observations on coronary sinus rhythm and its mechanism, Amer J Cardiol 7:198 1961
4. Mirowski M Left atrial rhythm. Diagnostic criteria and differentiation from nodal arrhythmia Amer J Cardiol. 1 :203, 1966.

Reply

To the Editor

I am very grateful to Dr Spodick for pointing out the purpose of our paper which is intended to call attention to the value and *limits* of the electrocardiographic diagnosis of "left atrial rhythm.

The modern studies of electrophysiology have indeed increased our knowledge on the other hand, they invite a greater carefulness in the electrocardiographic interpretation. The interpretation of the VCG which shows i a synthetic way the spatial orientation and temporal sequence of cardiac vec tors, is bound more directly to the cardiac activation, while the ECG's interpretation is analytic and often bound to separate findings.

This is why we thought it useful to report the characteristics and morphologic variability of the VCG in the so-called left atrial rhythm. They in fact, confirm by means of a simple clinical technique what had been experimentally demonstrated by Spodick and Colman and by Massumi and Tawak kol.

Eligio Piccolo M.D
Associate Professor of Medicine
Istituto di Clinica Medica
Cardiovascular Section
University of Padua Medical School
Padua, Italy

Book reviews

THE CORONARY CARE UNIT. By William J. Grace, M.D. and Victor Keyloun, M.D. New York, 1970, Meredith Corporation, 223 pages. Price $8.50.

Grace and Keyloun ha described their experience with their coronary care unit (C. C. U.) in a small nd useful book. Subjects discussed include the natural history of acute myocardial infarction, designs of coronary care unit, general therapy of myocardial infarction, management of ar rhythmias and cardiac arrest, nursing care, and other important aspect of the operation of such unit. The proper construction nd equipping of such unit is extremely important but still not nearly as important as the ability of all the people who ork in the unit. The operations dangers and hazard re well recognized by the uthors, as they clearly describe these aspects of the C. C. U. This short book should interest nurses, physicians, residents, interns, and tudents. Unfortunately the authors (as th many modern practices) use such terms as first degree block, etc. This is not preferred practice, for it is much more accurate to refer to the duration of the P R interval itself. A P R interval of 0.60 sec. is much worse than one of 0.22 sec., although both are first degree block. A P R interval can change and still be a first degree block. A P R interval that changes from 0.60 sec. to 0.24 sec., better described in units of time rather than merely that first degree block, is still present. Nevertheless, this is useful book hich requires profound knowledge of cardiology not only to be appreciated adequately but lso to be employed in the best of cardiologic practice.

BRADYKININ AN RELATED KININS. Cardiovascular Biochemical and Neural Actions, Advances in Experimental Medicine and Biology Vol. 8. Edited by F. Sicuteri, M. Rocha e Silva, and N than Back, New York, 1970, Plenum Press. 651 pages. Price $27.50.

The proceedings of an international symposium held in Florence, Italy during July 21 to 25 1969 summarize very well the present status of physiologic and pharmacologic actions of bradykinin and related kinins. There were many contributors and there was worldwide representation of nations. Seventy-seven separate presentations are included in this compendium which covers extensively the subject of kinins. Everyone in physiology or pharmacology as well as those interested in the circulation, ill find the papers worth careful reading. The book consists of short papers summarizing studies from the respective l the meth d the results hort bibliog raphy is ppended t ach presentation. This is a good presentation of the proceedings for those who were unable t ttend the ymposium.

CARDIOVASCULAR DY AMICS, ed. 3. By Robert F. Rushmer, M.D. Philadelphia 1970, W. B. Saunders Company. 559 pa es. Price $18.50.

Rushmer third edition of *Cardiovascular Dynamics* is intended primarily for undergraduat medical students and those who are learning cardiovascular physiology nd clinical medicine. H has engaged the assistance of some of his clinical colleagues t assist ith the clinical presentations. T write bout the normal and abnorm l physiology of the entire cardiovascular sy tem is almost an impossible task. However Rushmer has se lected aspect of the many problem and presented his ow ideas and concepts. He avoided entering controversial discussions or concepts. This will be acceptable to the reader long as he realizes that other theories nd interpretations do exist for almost every discussion included in this book. The subject considered are co plex, g. congestive heart failure efficiency of the heart, production of heart sound and mur murs, and many others. Rushmer nd his associates ha simplified the concepts with clear line dr ings, but everyone know that these simplifications do not describe the entire mecha nism. Nevertheless, this is good book. The data and thoughts presented are acceptable ones. Any book of this type is not only thought provoking but immediately suggests venues for research. Regardless of one opinions, those in the cardiovascular field should t least have knowledge of the contents of this book. The reader is warned that the cardiovascular dynamics and physiology are much more complex than outlined and our knowledge is more unknow than known. The bibliography is fairly ell selected but far from complete, hich is understandable since Rushmer and his associates present selected material and ideas and, therefore, selected the references ac cordingly. The origin and stimulus for the many concepts presented can be found in many other papers in the literature. This edition is good one which is recommended for careful, thoughtful, and concentrated reading.

SOURCES AND SURFACE REPRESENTATION OF THE CARDIAC ELECTRIC FIELD. Edited by Dr. Ivan Ruttkay Nedecky, CSc., and Eva Kellerova, Bratislava, Czechoslovakia, 1970. Publishing House of the Slovak Academy of Sciences. 425 pages.

This publication of the proceedings of the Seventh International Colloquium on Vectorcardiography held Sept. 13 to 16 1966, is of considerable in-

Letters to the editor

Left atrial rhythm

To the Editor

"Left atrial rhythm Vectorcardiographic study and electrophysiologic critical evaluation" by Piccolo and associates[1] is a nice analysis of the problem I would only object that despite their "better" theoretic basis vectorcardiogram (VCG) lead systems are no more conclusive than the electrocardiogram (ECG) in determining the precise location of a pacemaker However the authors have properly placed their data in the context of the relevant literature and thus support the conclusions of Massumi and Tawakkol's outstanding original studies.[2] In 1961 we published what appeared to be the first ECG series reporting the variable vector orientation of atrial activation in the horizontal plane in association with inverted P_{II} P_{III} and aV_F during coronary sinus rhythm.[3] The experimental literature even at that time permitted no fixed conclusion as to the site of the pacemaker The results of all these reports illustrate the hazards of excessive extrapolation in electrocardiography exemplified by certain studies on left atrial rhythm

Arrhythmia analysis has always invited the construction of great inverted pyramids in which a mass of "explication" must rest on one or two shaky assumptions. This has been an irresistible attraction for intellectual gamesmanship which, in fairness often does provide worthwhile mental calisthenics to at least sharpen our approach to the ECG However in considering this kind of study one must keep in mind that all the resulting "deductive" interpretations remain in limbo, subject to definitive investigation, i.e. studies done directly on the heart and if possible, in human beings. In the case of left atrial (LA) rhythm this has been done by Massumi and supported by Piccolo and co-workers who have avoided the trap of excessive intellectualization of the overworked electrocardiogram.

David Spodick M.D
Tufts University School of Medicine
Department of Medicine
Lemuel Shattuck Hospital
Boston, Mass

REFERENCES

1 Piccolo, E. Nava, Andrea, Furlanello, Francesco, Permutti, Bruno, and Dalla Volta, Sergio. Left atrial rhythm. Vectorcardiographic study and electrophysiologic critical evaluation, Amer. Heart J 80:11 1970.
2 Massumi R., and Tawakkol A. A. Direct study of left atrial P waves, Amer J Cardiol. 20:331 1967
3 Spodick, D H and Colman, R. Observations on coronary sinus rhythm and its mechanism, Amer J Cardiol :198, 1961
4 Mirowski, M Left atrial rhythm. Diagnostic criteria and differentiation from nodal arrhythmia, Amer J Cardiol. 17:203 1966.

Reply

To the Editor

I am very grateful to Dr Spodick for pointing out the purpose of our paper which is intended to call attention to the value and *limits* of the electrocardiographic diagnosis of "left atrial rhythm.

The modern studies of electrophysiology have indeed increased our knowledge on the other hand, they invite a greater carefulness in the electrocardiographic interpretation. The interpretation of the VCG which shows in a synthetic way the spatial orientation and temporal sequence of cardiac vectors, is bound more directly to the cardiac activation, while the ECG's interpretation is analytic and often bound to separate findings.

This is why we thought it useful to report the characteristics and morphologic variability of the VCG in the so-called left atrial rhythm. They in fact, confirm by means of a simple clinical technique what had been experimentally demonstrated by Spodick and Colman and by Massumi and Tawakkol.

Eligio Piccolo M.D
Associate Professor of Medicine
Istituto di Clinica Medica
Cardiovascular Section
University of Padua Medical School
Padua, Italy

American Heart Journal

February 1971 Volume 81 Number 2

Editorial

Revascularization of the heart—numerators in search of denominators

David H. Spodick, M.D.
Boston, Mass.

Physicians cure little or nothing. We alter physiology, arrest inflammation, and remove tissue, but with the exception of some infections and deficiency states there are few if any cures in terms of *restitutio ad integrum*. This situation is nowhere more evident than in coronary heart disease. We can do much with timely control of complications: dysrhythmias, congestive failure, angina. Yet we have not made significant inroads on the onset and evolution of the fundamental process, coronary atherogenesis, much less reversed established atheromas. Medical tactics and preventive strategies are hardly likely to improve in the short run as basic investigation continues to reveal multifold causes, from metabolic to psychogenic, of the atherosclerotic process and the physicochemical complexities of its development. The urgency of protecting life and health in this situation has long suggested that we bypass the basic process by a direct attack on its final common pathway: myocardial ischemia.

A succession of experimentally well-conceived and technically brilliant surgical attempts to neovascularize and revascularize the heart have done wonders in a variety of laboratory preparations. All have been announced enthusiastically and appear to perform well, at least initially, in human beings. For some, the supporting clinical evidence is anecdotal rather than statistical: "Selected cases" have improved[1-3] or peep-show reports of a handful of chosen survivors document their technical feasibility.[4-6] Series of others appear to show consistently improved morbidity and mortality rates when compared with previous experience or with patients said to represent comparable control groups.[7-9] Many procedures never became widely accepted and some have been largely abandoned even by their originators. Not one has escaped serious criticism on one ground or another: failure of laboratory studies to duplicate clinical conditions, failure to effectively revascularize myocardial tissue, or failure to give results equal to the initial studies. Conspicuously lacking has been criticism on the really crucial issue: *adequacy of the data to which their results are compared*. Now the earlier operations are upstaged by the appearance of techniques of greater promise: direct

From the Cardiology Division of the Medical Services, Lemuel Shattuck Hospital and the Department of Medicine, Tufts University School of Medicine, Boston, Mass.

Reprint requests to: Dr. D. H. Spodick, Lemuel Shattuck Hospital, 170 Morton Street, Boston, Mass. 02130.

*Chief, Cardiology Division, Lemuel Shattuck Hospital; Associate Professor of Medicine, Tufts University; Lecturer in Medicine, Boston University.

terest in that it summarizes very well some of the work being conducted at that time throughout the world. The subjects discussed are many, both technical and clinical. Among the many aspects of vectorcardiography presented were the lead systems, instrumentation, and physiology of the cardiac electric field in normal, pathologic, and clinical states. The presentations are concise and clear. Unfortunately, the informal discussion that must have transpired at the meetings were not included. These are often the most significant aspects of such scientific gatherings. Nevertheless, anyone interested in electrocardiography and vectorcardiography will find this publication to be of much interest even though the data are about one-half decade old.

THE TETRALOGY OF FALLOT from a Surgical Viewpoint. By John W. Kirklin, M.D. and Robert B. Karp, M.D., Philadelphia, 1970, W. B. Saunders Company. 189 pages. Price $13.00.

Dr. Kirklin and associates describe clearly and with excellent illustrations their own experiences with the surgical management of tetralogy of Fallot. Kirklin reviews briefly his approaches since beginning cardiovascular surgery at the Mayo Clinic in 1950. This monograph includes discussions of the nature of the lesion, the hemodynamic disturbances associated with it, its natural history, clinical manifestations, operative technics, results of surgery, and indications for surgery. The bibliography is extensive and the index is good. This book, by an outstanding cardiac surgeon, describes his experiences with a congenital disease about which he has made considerable important surgical contributions and has obtained excellent surgical results. This book is recommended to cardiologists as well as to cardiac surgeons.

individuals, shunted patients paid for hemostasis with some operative deaths and more metabolic toxicity so that the "funeral rate"* was quite steady. Here the particular lesson is that *correction of hemodynamics is not proof of net benefit to the patient*.

Fundamental need for appropriate design of trials

Faith is a state which rejects standards of comparison. Thus, the question "How is the wife?" when answered, "Compared to whom?" is funny because it contains implications which are supposed to be ignored. Physicians and surgeons, traditionally long on faith and short on science, can no longer have it this way: the strongest faith in the efficacy of a treatment cannot replace scientific standards for judging that treatment.

Properly designed controlled trials are aimed at providing denominators (standards of comparison) for the numerators (results) generated by treatment. *Without corresponding denominators, numerators have no objective existence* for any scientist and more critically so for physicians who need valid standards on humanitarian as well as scientific grounds. *New treatments can only be proposed by valid comparison with existing treatments or with no treatment* and can only be opposed by attacking the validity of that comparison. Valid comparisons can be set up only by minimizing conscious and unconscious bias.

Evaluation of therapy can be clearcut without elaborate design, e.g. life saving tactics in many emergencies or digitalis for heart failure. More often this is not so. Examples include the long- and short-acting medications for angina and the 20-year battle over the use of anticoagulants in coronary disease, although both kinds of treatment perform spectacularly in the hands of their developers. The question is always, *What would have happened in the same or truly comparable individuals under circumstances identical excepting for the treatment under study?* If, for example, comparable patients are worse with than without a given operation, they have undergone what is, in a sense, a well-intentioned assault and battery. It is no better if operated patients are unchanged as this may be due to preoperative selection of natural survivors. Moreover, temporary improvement in angina, dyspnea, or effort tolerance if paid for with increased deaths over control patients would indeed produce a technical *tour de force*—but a Pyrrhic victory. In fact there need be no real gain even with genuine remission after a particular coronary operation if its advocates have somehow chosen individuals already destined to improve (we may suspect this to be the common basis of certain successes in "selected patients"). These considerations make it imperative to raise and answer to the best of our ability the question "What are we *really doing?*" in acceptably controlled trials of new (and old) procedures by

(1) application of predetermined criteria both for inclusion in the series and for judging the results,
(2) appropriate numbers of concurrent control and operated patients, and
(3) *random assignment of patients to* operated and nonoperated groups.

Randomization is the key: it should distribute *both the known and the unknown variables between both groups*, minimizing conscious and unconscious bias in the allotment of patients. Randomization permits this crucial decision to be made by *chance* so that significant postoperative differences between operated and control patients should *not* be due to chance.

Rigid comparability would involve sham operations. Skin incisions alone did indeed appear to "cure" angina and improve function in trials against mammary artery ligation but this is hardly practical for simulating extensive surgery. Yet a form of sham operation seems to have been accomplished in patients with Vineberg implants who definitely improved despite occlusion of the implanted arteries.[1,29] Sad to note, one group reporting such improvement concluded simply that some other effect of the operation was responsible. Fair enough. But this neglects the alternate possibilities—in the absence of controls—that (1) patients were selected who might have improved anyway or (2) the patients might have done even better without the operation.

*That is, the actual population at risk.

anastomosis into the coronary tree of arteries and segments of arteries and veins These appear capable of giving rapid improvement and may well provide lasting benefits. Similar procedures have been successful in peripheral arterial disease It is therefore urgent to grasp the fresh opportunity to objectively establish the merits of direct coronary operations before they become more or less accepted as was the case with certain formerly and still popular procedures some of which inspired second thoughts only after large numbers of patients had received their dubious benefits

Traditionally physicians have been prepared to apply heroic measures in ominous circumstances but it is the patient who has been willy nilly the hero Valid proof of effectiveness should therefore be required of potentially dangerous procedures It has become unthinkable to accept most nonsurgical therapies without trials against comparable control populations Before a study of a new pill or injection can see the light of day the Food and Drug Administration granting authorities therapeutic trials committees and responsible journal reviewers demand appropriate design control groups and statistically convincing results. These approaches regularly raise serious doubts and frequently give the *coup de grâce* to many treatments which performed miracles in the hands of their originators. Equal standards demanded of each form of surgery for coronary heart disease might resolve its status (1) no improvement or worsening due to surgery—subsequently sparing large numbers of patients the mortal risk and discomfort of ineffective or harmful operations *or* (2) conclusive benefits—subsequently sparing large numbers of patients the mortal risk and discomfort of disease Now that technical advances permit the most promising approaches it is time to organize widespread appropriately designed and controlled studies lest one or another of the direct coronary operations become as established in the hands of their proponents as some older procedures have been Unfortunately although controlled trials appear to be living and well in Oteen N C [16] elsewhere the stampede is on Where will it lead to? Why are we reluctant to apply equal standards to all forms of therapy?

Where are they now?

Few surgical procedures have ever been subjected to appropriately designed clinical trials least of all perhaps, cardiac operations. Some of these have been quietly dropped by prudent surgeons because of an obviously unacceptable operative mortality rate or conspicuous lack of benefits.[illegible] Simple coronary endarterectomy for example recognition of its snowplow effect on the arterial branches came a bit late.[illegible] On the other hand internal mammary artery ligation was finally subjected to controlled trials but only after being visited upon large numbers of patients with enthusiastic claims of successful results[14] Indeed laboratory reports had indicated 80 per cent survival after coronary occlusion in operated animals[14] increased delivery of blood to the myocardium[13] and claims of benefits to as high as 95 per cent of patients [14,15] Unfortunately for this safe, simple cheap procedure sham operations achieved an equal number of symptomatic functional and electrocardiographic remissions [16,17] One lesson of this experience is that *results in some laboratory animals may not be translated into benefits to patients.* Even more important is the parallel with so many medicinal cures wild success finally deflated by carefully controlled observations.

Popular noncardiac operations regularly disappear The vogue for gastropexy and tacking into place of assorted other organs is receding into the dim past Routine circumcision and tonsillectomy performed in their millions remain controversial Glomectomy for asthma was so enthusiastically proffered by its originators that a respected Boston newspaper proclaimed ASTHMA CURED in banner headlines Controlled trials killed glomectomy

An important example is prophylactic portacaval shunt to prevent bleeding from esophageal varices. The results in uncontrolled series were spectacular patients did not bleed again and catheterization showed that the portal system was indeed decompressed—success! Unfortunately when compared to truly comparable unoperated

individuals shunted patients paid for hemostasis with some operative deaths and more metabolic toxicity so that the funeral rate"[*] was quite steady. Here the particular lesson is that *correction of hemodynamics is not proof of net benefit to the patient.*

Fundamental need for appropriate design of trials

Faith is a state which rejects standards of comparison. Thus the question "How's the wife?" when answered "Compared to whom?" is funny because it contains implications which are supposed to be ignored. Physicians and surgeons, traditionally long on faith and short on science, can no longer have it this way: the strongest faith in the efficacy of a treatment cannot replace scientific standards for judging that treatment.

Properly designed controlled trials are aimed at providing denominators (standards of comparison) for the numerators (results) generated by treatment. *Without corresponding denominators numerators have no objective existence* for any scientist and more critically so for physicians who need valid standards on humanitarian as well as scientific grounds. *New treatments can only be proposed by valid comparison with existing treatments or with no treatment* and can only be opposed by attacking the validity of that comparison. Valid comparisons can be set up only by minimizing conscious and unconscious bias.

Evaluation of therapy can be clearcut without elaborate design, e.g., life-saving tactics in many emergencies, or digitalis for heart failure. More often this is not so. Examples include the long- and short-acting medications for angina and the 20-year battle over the use of anticoagulants in coronary disease, although both kinds of treatment perform spectacularly in the hands of their developers. The question is always, *What would have happened in the same or truly comparable individuals under circumstances identical excepting for the treatment under study?* If, for example, comparable patients are worse with than without a given operation they have undergone what is, in a sense, a well-intentioned assault and battery. It is no better if operated patients are unchanged, as this may be due to preoperative selection of natural survivors. Moreover, temporary improvement in angina, dyspnea, or effort tolerance if paid for with increased deaths over control patients would indeed produce a technical *tour de force*—but a Pyrrhic victory. In fact there need be no real gain even with genuine remission after a particular coronary operation if its advocates have somehow chosen individuals already destined to improve (we may suspect this to be the common basis of certain successes in selected patients). These considerations make it imperative to raise and answer to the best of our ability the question "What are we *really* doing?" in acceptably controlled trials of new (and old) procedures by

(1) application of predetermined criteria both for inclusion in the series and for judging the results,
(2) *appropriate* numbers of concurrent control and operated patients, and
(3) *random assignment* of patients to "operated" and "nonoperated" groups.

Randomization is the key: it should distribute both the known and the unknown variables between both groups, minimizing conscious and unconscious bias in the allotment of patients. Randomization permits this crucial decision to be made by *chance* so that significant postoperative differences between operated and control patients *should not* be due to chance.

Rigid comparability would involve sham operations. Skin incisions alone did indeed appear to "cure" angina and "improve" function in trials against mammary artery ligation but this is hardly practical for simulating extensive surgery. Yet a form of sham operation seems to have been accomplished in patients with Vineberg implants who definitely improved despite occlusion of the implanted arteries.[39] Sad to note, one group reporting such improvement concluded simply that some other effect of the operation was responsible. Fair enough. But this neglects the alternate possibilities —in the absence of controls—that (1) patients were selected who might have improved anyway or (2) the patients might have done even better without the operation.

*That is, the actual population at risk.

Since most operations for coronary disease have been well conceived without properly designed trials their value can neither be confirmed *nor denied* they are entitled only to a Scottish verdict Not proven Moreover even if operated and control groups were to show statistically equal benefits this might have occurred in biologically different patients proper design should then disclose any such substrata of patients who could in fact benefit from surgery i e any valid success should produce valid criteria for patient selection Substratification could also define the actual objectives of a particular operation for particular patients relief of angina improvement of myocardial function prolongation of life But we cannot proclaim any of these benefits even for selected cases *unless we select them fairly*

Suitably designed controlled trials have radically changed drug therapy by providing methods of obtaining and viewing the results of treatment with a minimum of distortion In the surgical laboratory the use of control animals is standard practice Urging the same standards for coronary surgery in human beings should be a matter of preaching to the converted *Why is this not so?* What are the barriers to accepting controlled clinical trials?

Barriers to acceptance of controlled trials

It's not so much what we don't know that causes trouble as what we know that ain't so —Will Rogers

Burgeoning programs of myocardial revascularization are in the hands of cardiologists and surgeons of the highest technical and professional expertise. Therefore it is alarming to read certain explanations for omitting control patients for example "because of the multiple variables randomly selected patients cannot serve as adequate controls except in an extremely large series." [n] But the size of the job should never abort the search for truth And as we have seen randomization is inescapable precisely *because of* variability The assertion cited is the more remarkable when we realize that it emanates from one of the world's busiest revascularization teams

Clearly the barriers to accepting controlled trials are conceptual and not related to skill or intellect They form an interlocking set of vices and misapplied virtues

BARRIERS TO ACCEPTANCE OF ADEQUATELY CONTROLLED TRIALS

- A Human attributes
  - 1 Faith
  - 2 Advocacy
  - 3 Impatience
- B Statistical delusions
  - 1 Numerators
    - a Small sample
    - b Large sample
  - 2 Denominators Inadequate standards
- C Professional attributes
  - 1 Olympianism
  - 2 Clinical experience
  - 3 Testimonialism
  - 4 Extrapolation
  - 5 Activism
  - 6 Ethics

Human attributes

Certain of the characteristics which cardiologists share with all mankind are necessary in some degree for our self-confidence Beyond this they get in our way

Faith Without belief in most of our treatments, physicians could not function effectively *Faith* implies not only belief but also the suspension of disbelief and (as we have seen) this requires the rejection of standards of comparison The abiding faith of yesterday's bleeders and purgers in their efforts hardly make their methods more acceptable to us. We still feel ethically bound to use a treatment if we believe it works Yet omitting to demand adequate proof converts belief to simple faith or rather credulity which is conceptually at least on a par with that of the bleeders and purgers

Advocacy Few treatments succeed as well as they do in the hands of their originators Here Invention too often becomes the mother of Necessity introduction of a new treatment seems to require its protracted defense against all comers. Even after contrary results begin to appear those who develop a new medical or surgical therapy rarely issue negative reports. If even without a control series, their results obviously sour as time and more patients pass on the treatment is quietly dropped If not, enthusiasm leads to larger and larger series which brings such faith in the method that a valid control series becomes unthinkable [n] as has been the case among many

advocates of anticoagulant therapy.[23] Advocacy makes us reluctant to murder our own progeny.

Impatience. It has been held that a properly designed and controlled trial would (1) take too long, (2) require too many patients or (3) both, or (4) it has its own imperfections, so why bother? *Impatience* is, of course, a result of faith in and advocacy of what we are already doing. This is the shakiest of all barriers, a set of excuses, pure and simple. We cannot wait to confer our new blessing on humanity. In the case of coronary surgery the stakes are particularly high—we should be quite prepared to take the same time to operate on half the number of patients or take twice the time to do the same number as we would have in an uncontrolled series, despite any eagerness to "get on with it." Finally, the impracticality of blinding or of sham operations may be offered as sufficient excuse for rejection of a control group. Even the best designed trial must have imperfections, but these can only be *less than in an uncontrolled trial.* Indeed the objective of careful design and control is to do as well as possible, i.e., to *minimize* error. No dice can be made with absolute precision, yet no one will dispute that we get better probabilities from an honest than from a loaded pair.

Statistical delusions

Successes ascribed to one or another treatment of myocardial ischemia are based on some kind of numerical comparison between those who have had it and those who have not or with the patients as their own controls. If the numbers looked good they were considered to be, in themselves, proof of success. Other such results are tabulated and described along with the cabalistic symbols of the statistician. Imprimatur! Unfortunately, the most elaborate statistical manipulation will not produce a good result from a bad design.

Small sample. A 60 per cent success rate would appear impressive. But if this means that 60 of 100 patients survived a procedure and appeared to improve we are more impressed than if it refers to three out of five patients because the next five patients could go one way or the other. Sufficiently large series minimize the effects of individual variability by ensuring better distribution between operated and control patients. This point—small sample variability—is instinctively (if not statistically) appreciated by most cardiologists. But anecdotal reports continue to appear.

Large sample. Belief in the power of large numbers per se is rampant compared with the small sample delusion (for example the very large cooperative trial of anticoagulant therapy in patients with myocardial infarction).[4] In certain quarters its impressive figures made it virtually a malpractice to omit anticoagulants.[23,24] Since then, well designed trials have cast doubt upon the results.[25,27] The most charitable verdict is that the place, if any, of anticoagulants in treating coronary disease remains uncertain. Large numbers cannot salvage a flawed plan. Multiplying zero even by a million would leave us with zero—you can arrange a million zeros in interesting patterns, but numerically they will not budge.

Inadequate standards. It is plain that results without some standard of comparison are as meaningless as numerators without denominators. But with the *wrong denominators* they may be worse than meaningless, in fact downright misleading. The specific effects of insulin and vitamin B_1 are so clear that we can rely on past experience for our standard. So far this certitude escapes us in the case of medical or surgical therapy for ischemic heart lesions. Attempts to label results as improvements over the "natural history" of the disease, over projected mortality rates or retrospective experience with symptoms and function, regularly lead to initial success and later to conflicting reports. Even honest attempts at a control series may founder on the rocks of conscious and unconscious bias, as is likely in series which ignore randomization. For example, the kind of plan used in the American Heart Association cooperative study of anticoagulants in acute myocardial infarction[4] assignment of patients by alternate day to treatment and control groups. Referring physicians who have *prejudged* treatment to be superior to "no treatment" might then hold good risk patients for the days on

which the treatment is given Conscious bias thus can sneak in (for the investigators of course this is unconscious bias) Since admission of sicker patients cannot be delayed they would tend to distribute evenly on each day In the anticoagulant study the mortality rate was 23 4 per cent in the control group and 16 per cent in the treated group [24] Since death is an undisputed end point this difference appears to be especially impressive It is impossible to determine to what extent bias of any kind may have produced the difference but its validity is challenged by subsequent studies which included random allotment of patients [26,27] Thus the results of the game depend on how we play it To obtain denominators that correspond to our numerators the rules must be tightly drawn to minimize any opportunity—deliberate or accidental—to load the dice

Professional attributes

Cardiologists are prima donnas We cope daily with dramatic challenges we deal with an organ in which our tests and treatments yield all kinds of numbers cardiac responses can be measured in milliseconds All of this inspires great self-confidence Each of us moreover suspects that he has a unique mastery of the stethoscope and is quite certain that he can interpret the electrocardiogram better than anyone else in the vicinity These spring from traditional attributes of the physician which seem particularly keen in cardiologists and surgeons They have been perhaps the strongest barriers to accepting the possibility that we may not have an inbred if not inborn ability to objectively evaluate our efforts.

Olympianism The loftily self sufficient doctor is convinced that he is a uniquely qualified judge of his own decisions, which therefore require little or no outside assistance His efforts are ultimate efforts This traditional godlike self image is abetted by the adulation of the traditional dependent patient In recent years olympianism may be weakening but in many successful physicians and surgeons it blocks their receptivity for dangerous ideas i e those which raise doubts.

Clinical experience Napoleon had two mules They had seen a hundred campaigns but they were still mules. Physicians may be somewhat better equipped to learn from what they see and feel yet individual experience is haphazard and none can escape its effect on personal decisions. Even group experience can lead to erroneous conclusions because some fact or the result of some methods are considered obvious. The benefits of surgically bypassing coronary narrowing would appear obvious, if we are to believe the testimony of our eyes. This could indeed be so but the history of medicine continues to reveal that very little is either simple or obvious and that we must ask for convincing proof Anticoagulants, for example were the obvious answer to myocardial infarction because it was obvious that thrombi caused infarcts. Yet the effectiveness of anticoagulant therapy is at best highly questionable owing to well designed controlled trials [26,27] Moreover thrombi may not after all be necessary to initiate infarcts [18,31] indeed they may be the *result* of infarction in many cases.[28]

One common basis for opposing the assignment of patients to control groups may be epitomized How can I deny my patient a treatment that I *know* (i e that my experience tells me) works? Benjamin Rush treated yellow fever by venesection and massive doses of calomel with jalap. He first tried this surreptitiously in a patient he judged to be moribund This man somehow survived and when Rush himself developed the disease he took his own medicine [25,29] Rush *knew* that this therapy worked he applied and promoted it ardently in the Philadelphia epidemic No one can fault his intentions which arose from his clinical experience Well meaning attempts still begin with clinical experience yet it is the patient's road that we pave with our good intentions If we are to march him down this road at scalpel point we must *begin* with adequate controls—and not only in the dog lab

Testimonialism Faith healers and cancer quacks can always produce witnesses who testify to cure Physicians are aware of the healing power of psychologic maneuvers and the partial or total placebo effect of almost any therapy on symptoms like angina Angina indeed may improve spon

taneously or owing to severing nerves during surgery In either case providing testimony to postoperative improvement.

Physicians sometimes match the patient's credulity by uncritical acceptance of the advice of authorities as long as it is published somewhere or publicly spoken. We may extend this so far as to misinterpret the evidence of our own senses. In examining patients for example generations of cardiologists have recorded items like "P_2 greater than A_2" referring to the *location* of a *unitary* second heart sound. What they actually listened to was something else but what they were quite sure they heard was the result of indoctrination by standard practice the "Emperor's New Clothes" diathesis. Now that the situation has been set right, we hear the identical sounds, but correctly note their components. Similarly we often believe that treatments work because of our colleagues' anecdotes, or we accept case reports and unsubstantiated series, as long as they are in print. Moreover patients tell us they feel better (which is, in truth one desired result) This kind of evidence might in fact be soundly based but without valid comparisons it is testimonial evidence. In fairness, we sometimes have nothing better if it is the only game in town it is the one everyone plays. But this need not be so with coronary surgery.

Extrapolation. A trap for the unwary is extrapolation of results from one setting to another which may not be genuinely comparable The most pernicious form of unwarranted extrapolation is the uncritical transfer of experimental laboratory results to clinical practice Successful coronary surgery in dogs is, indeed a prerequisite for its application in human beings. Even judged against dog controls the results are not always good[23,24] In any case we know a priori that (1) the myocardium pericardium and coronary circulation of the dog differ from the human (2) the dogs studied are not atherosclerotic, and (3) coronary artery ligation and even ameroid constrictors do not closely duplicate the kinds, distributions, and durations of narrowing in the human coronary tree. Thus, success in the dog lab is only technically transferable to the operating room

Another form of extrapolation involves equating success with human test results after coronary surgery It is a joy to verify postoperative patency of implanted and anastomosed vessels, regional improvement in lactate metabolism etc. But this is not the same as clinical success. We must recall the portacaval shunt result hemodynamic correction but no change in funeral rate We should be further cautioned by certain experiences with Vineberg implants patients with *occluded* implants can do extremely well[1,25] implants may only appear to be patent because of high pressure injection of contrast medium[26-3] even patent implants may not deliver significant blood flow[31] patients can improve despite lack of either angiocardiographic or metabolic evidence of a successful implant[32,11,42] relief of angina subsequent infarct and death rates can be unrelated to patency[33] test occlusions of implanted vessels may not affect the electrocardiogram[34] the left ventricular function curve[35] or myocardial metabolism[42]

Activism Cardiologists are always prepared to act because of the immediate and *potential threats to their patients.* Surgeons *must be* by definition doers. But, unlike mountain climbers, cardiologists need not perform simply "because it's there" no treatment is sometimes as good as or better than certain therapies. Samuel Hahnemann's homeopathy saved many *thousands of lives* by prescribing infinitesimally small doses, in effect an enormous (though unappreciated) control series. Hahnemann died a millionaire because it was recognized that so many of his patients survived Although he believed that his extreme dilutions and triturations really worked, what Hahnemann did was to spare his patients the lethal remedies of his orthodox colleagues. One cannot argue that modern physicians are as purblind as those of Hahnemann's day One can argue that we must settle the issue of whether a given operation is better than nothing by doing nothing in half the cases or whether it is better than existing therapy by giving the patient a "50-50 chance" to have the operation or some other treatment. *The compulsion to treat* ("Doctor don't just stand there do something!") *should not be determined only by a need for*

which the treatment is given. Conscious bias thus can sneak in (for the investigators of course this is unconscious bias). Since admission of sicker patients cannot be delayed, they would tend to distribute evenly on each day. In the anticoagulant study the mortality rate was 23.4 per cent in the control group and 16 per cent in the treated group.[21] Since death is an undisputed end point, this difference appears to be especially impressive. It is impossible to determine to what extent bias of any kind may have produced the difference, but its validity is challenged by subsequent studies which included random allotment of patients.[26,27] Thus, the results of the game depend on how we play it. To obtain denominators that correspond to our numerators the rules must be tightly drawn to minimize any opportunity—deliberate or accidental—to load the dice.

Professional attributes

Cardiologists are prima donnas. We cope daily with dramatic challenges; we deal with an organ in which our tests and treatments yield all kinds of numbers; cardiac responses can be measured in milliseconds. All of this inspires great self-confidence. Each of us, moreover, suspects that he has a unique mastery of the stethoscope and is quite certain that he can interpret the electrocardiogram better than anyone else in the vicinity. These spring from traditional attributes of the physician which seem particularly keen in cardiologists and surgeons. They have been perhaps the strongest barriers to accepting the possibility that we may not have an inbred if not inborn ability to objectively evaluate our efforts.

Olympianism. The loftily self-sufficient doctor is convinced that he is a uniquely qualified judge of his own decisions, which therefore require little or no outside assistance. His efforts are ultimate efforts. This traditional godlike self image is abetted by the adulation of the traditional dependent patient. In recent years olympianism may be weakening, but in many successful physicians and surgeons it blocks their receptivity for dangerous ideas, i.e., those which raise doubts.

Clinical experience. Napoleon had two mules. They had seen a hundred campaigns but they were still mules. Physicians may be somewhat better equipped to learn from what they see and feel, yet individual experience is haphazard and none can escape its effect on personal decisions. Even group experience can lead to erroneous conclusions because some fact or the result of some methods are considered "obvious." The benefits of surgically bypassing coronary narrowing would appear obvious, if we are to believe the testimony of our eyes. This could indeed be so, but the history of medicine continues to reveal that very little is either simple or obvious and that we must ask for convincing proof. Anticoagulants, for example, were the "obvious" answer to myocardial infarction because it was "obvious" that thrombi caused infarcts. Yet the effectiveness of anticoagulant therapy is at best highly questionable owing to well-designed controlled trials.[26,27] Moreover, thrombi may not, after all, be necessary to initiate infarcts[29,31]; indeed they may be the *result* of infarction in many cases.[30]

One common basis for opposing the assignment of patients to control groups may be epitomized: "How can I deny my patient a treatment that I *know* (i.e., that my experience tells me) works?" Benjamin Rush treated yellow fever by venesection and massive doses of calomel with jalap. He first tried this surreptitiously in a patient he judged to be moribund. This man somehow survived and when Rush himself developed the disease he took his own medicine.[32,33] Rush *knew* that this therapy worked; he applied and promoted it ardently in the Philadelphia epidemic. No one can fault his intentions, which arose from his clinical experience. Well-meaning attempts still begin with clinical experience; yet it is the patient's road that we pave with our good intentions. If we are to march him down this road at scalpel point, we must *begin* with adequate controls—and not only in the dog lab.

Testimonialism. Faith healers and cancer quacks can always produce witnesses who testify to cure. Physicians are aware of the healing power of psychologic maneuvers and the partial or total placebo effect of almost any therapy on symptoms like angina. Angina indeed may improve spon-

emic heart disease, Angiology 12:333 1961

11. Dilley R. B Cannon, J A., Kattus, H A., MacAlpin, R. N and Longmire, W P.. The treatment of coronary occlusive disease by endarterectomy J Thorac. Cardiovasc. Surg. 50:511 1965
12. Effler D A., Groves, L. K., Sones, F M J and Shirey E. R. Endarterectomy in the treatment of coronary artery disease, J Thorac. Cardiovasc. Surg 47:98, 1964.
13. Proudfit, W L. Therapeutic procedures for angina pectoris, Dis. Chest 55:271 1969
14. Battezzati, M Tagliaferro, A and Cattaneo, A D Clinical evaluation of bilateral internal mammary artery ligations as treatment of coronary heart disease, Amer J Cardiol. 4 180, 1959
15. Dreyina, A. L: Clinical and experimental grounds for bilateral ligation of internal mammary arteries in chronic coronary insufficiency Vestn. Khir Grekov 81:94 1960.
16. Cobb, L. A Thomas, G. L, Dillard, D H Merendino, K. A., and Bruce, R. A An evaluation of internal mammary artery ligation by double-blind technique, New Eng J Med. 260:1115 1959
17. Dimond E. G., Kittle, C F and Crockett, J E. Comparison of internal mammary artery ligation and sham operation for angina pectoris, Amer J Cardiol. 5:483 1960.
18. Grace, N D Muench, H and Chalmers, T C. The present status of shunts for portal hypertension in cirrhosis, Gastroenterology 50:684, 1966.
19. Chalmers, T C. Mortality rate *versus* funeral rate in clinical medicine, Gastroenterology 46 788, 1964
20. Harken, D E Black, H Dickson, J F and Wilson, H. E. De-epicardialization simple, effective surgical treatment for angina pectoris, Circulation 12:955 1955
21. Proudfit, W L., Sones, F M Shirey E. K., Ferguson, D and Sheldon, W C. Revascularization of the myocardium, Dis. Chest 55:315, 1969
22. Fitzgibbon, G. M Hooper G D and MacIver D A Vineberg operation for myocardial ischemia preliminary report, Canad. J Surg 13 135, 1970.
23. Berryman, G H et al (co-operative study) Sodium heparin vs. sodium warfarin in acute myocardial infarction, J A M A 189:553 1964
24. Wright I S Marple, C. D., and Beck, D E. Myocardial infarction—Clinical manifestations and treatment with anticoagulants: A study of 1031 cases, New York, 1954 Grune & Stratton, Inc.
25. Griffith G. C and Boggs, R. P T withhold anticoagulants in the management of patients with myocardial infarction is to impair their prognosis, Controversy in internal medicine, Philadelphia, 1966, W B Saunders Company p. 105.
26. Seaman, A. J Griswold H. E., Reaume R. B and Ritzman, L. W Prophylactic anticoagulant therapy for coronary disease J A M A 189 183 1964
27. Hilden, T Iversen, K., Raaschou, F and Schwartz, M Anticoagulants in acute myocardial infarction, Lancet 2:327 1961.
28. Powell, J H.: Bring out your dead Harrisburg 1949 University of Pennsylvania Press.
29. Middleton, W S. The yellow fever epidemic of 1793 in Philadelphia, Ann. Med Hist. 10 434 1928.
30. Roberts, W and Buja, L. M.. The prevalence and significance of thrombi in coronary arteries in fatal acute myocardial infarction, Ann. Intern Med. 72:781 1970
31. Likoff W Segal, B. L., and Kasparian, H.: Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease New Eng. J Med. 276 1063 1967
32. Malett W G., Schroeder B and Tait I B Demand" and internal mammary artery implantation, Circulation 35 (Suppl 1) 152, 1967
33. Schiller U and Krepp S Ueber die Bedeutung experimenteller operationen erfahren zur Revascularisation des Myokards, Thoraxchir Vask. Chir 16 189 1968
34. Ekestrom, S., Ovenfors, C. O and William-Olson, G. Experiences of revascularization procedures for angina pectoris Scand. J Cardiovasc. Surg 1 105 1967
35. Vineberg A., Defries, T and Pablo, G. The Ivalon sponge procedure for myocardial revascularization, Surgery 4 1268 1968.
36. Zimmerman, H. A. The dilemma of surgery in the treatment of coronary artery disease, Amer. Heart J 77:577 1970.
37. Dart, C H., Kato, Y Scott, S. M Fish R. G., Nelson, W M., and Takaro, T : Internal thoracic (mammary) arteriography J Thorac. Cardiovasc. Surg 59 117 1970.
38. Dart, C H., Scott, S Fish R., and Takaro, T.. Direct blood flow studies of clinical internal thoracic (mammary) arterial implants Circulation 41 (Suppl. II) 64 1970.
39. Balcon, R., et al.. Letter Lancet 1 724 1970
40. Amery A., Roeber G., Vermoelen, H. J and Verstraete, M Single-blind randomized trial comparing heparin and streptokinase treatment in recent myocardial infarction, Acta Med. Scand. (Suppl. 505) 1969
41. Rosenak, H. I Medical vs. surgical therapy for angina pectoris, Dis. Chest 55:269 1969
42. Kaiser G. C., Barner H. B., Jellinek, M Mudd, J G and Hanlon, C. R.. Metabolic assessment of internal mammary artery implantation in the dog Circulation 41 (Suppl. II) 49 1970.

treatment it depends also on the effectiveness and safety of the treatments available

Ethics Ethical implications has been cited as an objection to withholding treatment from control patients who would qualify for myocardial revascularization.[39] This is an old chestnut It raises again (in a new context) the question of faith How can I deny my patient a treatment I *know* works? Again the crux of the matter is the word know and we are back to Square One without valid standards we cannot *know* we can only have faith and we have seen where this can lead Benjamin Rush was acting perfectly ethically because he *knew* that drastic purging and exsanguination cured yellow fever The notion that it is unthinkable to deny a patient a new treatment on ethical grounds spares the physician from feeling guilty for withholding a favored remedy In this way ethics saves the physician s soul but what of the patient s body?

The considerable disagreement among advocates of competing therapies for ischemic heart disease[34,40,41] makes clear that its treatment—medical and surgical—has not provided the kind of answers we find in judging insulin vitamin B_{12} and penicillin The professional quality and technical skill of the disputants is not in question The basis of their evidence and beliefs is In these circumstances it is clear that patients must be given a fair chance *not* to have a particular operation Therefore if ethics means keeping the patient s welfare foremost at all times the scientific approach and the humanitarian approach are one—*ethical conduct requires adequately designed and controlled trials*

Summary and conclusions

1 Medical therapy has not yet fundamentally affected atherosclerotic heart disease
2 Experimentally well-conceived and technically brilliant surgical revascularization procedures raise great hopes for symptomatic and functional improvement and perhaps decreased mortality rates.
3 Without adequately designed controlled trials including random allocation of patients the merit of new and old revascularization procedures are neither established nor negated
4 Since there is no lack of intellect or skill barriers to acceptance of adequately controlled trials are conceptual. They include human and professional characteristics and statistical misconceptions.
5 Favorable laboratory results are important in suggesting the value of a procedure but have little validity in judging its achievements, whether they be prolongation of life or improvement in symptoms or function
6 Surgical treatment is not inherently beneficial because it is mechanical. All therapies must be judged by their results. The natural referees of medicine—granting authorities, therapeutic trials committees, and journal reviewers—should demand of surgical therapies the same standards that they demand of drug therapy
7 On both scientific and ethical grounds, controlled trials are due as soon as technical feasibility is demonstrated

REFERENCES

1 Bakon, K Leaver D Ross, D Ross, K., and Sowton F Clinical evaluation of internal mammary implantation Lancet 1:440 1970.
2 Beck, C S and Leighninger D S Operation for coronary artery disease A n. Surg 141:24 1955
3 Beck, C S. The coronary problem. A definition and an answer J Pakistan Med. Ass. 6:16, 1956.
4 O Shaughnessy L Surgical treatment of cardiac ischemia, Lancet 1 185, 1937
5. Bailey C P May A. M and Lemmon, W M. Survival after coronary endarterectomy in man, J A M A. 164:641 1957
6 Beck, C S. St nton E Batiuchok, W and Leiter E. Revascularization of heart by graft of systemic artery into coronary sinus, J.A.M.A. 137 436 1948
7 Mozen, H E. The treatment of coronary artery disease by surgical operation, Surgery 4 394 1957
8 Wolfso S Amsterdam E. A and Gorlin, R. Prognostic significance of angina therapy Preliminary report, Circulation 36:(Suppl 2) 274, 1967
9 Gorlin, R Myocardial revascularization with internal mammary artery implantation J.A.M A. 207:907 1969
9a. Takaro, T Personal communication May 14 1970
10. Marel, M S. and Bolton E. Cardiopery versus endarterectomy in the treatment of isch

disease Their ages ranged from one to 15 years. Older normal children were selected at their annual school physical examination, while younger ones were selected at the time of outpatient evaluation preceding minor operations other than tonsillectomy History taking routine physical examination cardiac roentgenogram and standard 12 lead plus V_{3R} electrocardiograms were done on every case. Diagnoses in cardiac patients were confirmed by right heart catheterization in some and at the time of operation or autopsy in others. Atrial septal defect, ventricular septal defect (VSD) patent ductus arteriosus (PDA) tetralogy of Fallot (TF) and pulmonic stenosis (PS) with intact ventricular septum were the most common defects, and the incidence of isolated T wave inversion in th precordial leads was studied in each group. Cases with arrhythmias conduction defects, or congestive heart failure with or without digitalization were excluded from the study Electrocardiograms were not taken in the postprandial period Frank lead vectorcardiograms were also taken in all with the precordial electrodes at the fourth intercostal space. The duration of the ST T complex was measured in II standard limb leads to determine its duration and to include isoelectric segments into the analysis.

The exact precordial mean ST T potential distribution and subsequently the null line were determined with Fukuda DW 1T model in 15 individuals in each age group of normal children and in 20 cases each of ASD VSD PDA, and TF and in 5 cases of PS A grid system was employed to explore the entire precordium with each electrode location 2 0 cm. apart both laterally and longitudinally (including the diameter of the electrode) Special caution was taken along the null line or near V to V_4, in which location recordings were taken 1.0 cm. apart instead of 2.0 cm.

Deep inspiration was done during the recording along the null line at varying horizontal levels to clarify its effect on the shape and potential of the T wave and subsequent dislocation of the null line.

*Fukuda Medical Electronics Company, Ltd Japan.

Results

Isolated T wave inversion was encountered in one per cent of normal children of both sexes, one through 15 years of age (Table I) At all ages, the lead in which the T wave was isolatedly negative was generally V In younger children however the negative T extended to V_4. Findings were different in electrocardiograms of children with congenital heart disease. Generally the isolated inverted T waves extended to a wider range and to the left in ASD VSD and PDA. In isolated PS and TF isolated T-wave inversion was rare but it was found in over one half of the ASD cases and in over 20 per cent of the PDA and VSD cases. Among 12 patients with VSD with isolated T wave inversion to the left of V_4 11 had a right ventricular peak systolic pressure higher than 35 mm. Hg and in 8 of them this pressure exceeded 70 mm Hg In 10 patients with PDA and isolated T-wave inversion 6 showed a peak right ventricular systolic pressure over 35 mm. Hg and 2 of them had a significant bidirectional shunt.

Grant and associates defined simulated isolated T wave negativity as those isolated T-wave inversions which were explained by the direction of the mean T wave vector and interrelation of lead locations with the null line slope (Fig 1) T_{II} and T_{VF} are assumed to be negative from the direction of the mean T wave vector Simulated isolated T-wave negativity was searched for among those with isolated T wave inversion. None of the normal children however manifested inverted T_{II} and T_{VF} at the same time, irrespective of the presence or absence of isolated T wave inversion Among those with congenital cardiac defects, one with ASD had negative T_{II} and T_{VF} at the same time, but no associated isolated T wave inversion. Mean T wave vectors were not oriented upward in any of these patients with isolated T-wave inversion.

Although the experimentally obtained null line in normal children varied individually the general pattern was similar in normal children of the same age. The pattern changed with age in accordance with the juvenile negative T wave pattern over the precordium The null line of mean

Clinical communications

Isolated T-wave inversion in the electrocardiogram of children

Shoichi Iwa, M.D.
Leonard M. Linde, M.D.
Masahiro Oshima, M.D.
Kazuo Momma, M.D.
Norimasa Nakamura, M.D.
Masayoshi Yanagisawa, M.D.
Katsuya Yoshino, M.D.
Tokyo, Japan, and Los Angeles, Calif.

Modern electrocardiographers have accumulated vast empirical clinical information and have now come to the era of re-evaluation of a more fundamental basis. One problem, the evaluation and management of the nondipolar component of precordial leads, has been approached by vectorcardiography with newer orthogonal corrected lead systems.[1-4] Traditional scalar electrocardiography, on the other hand, gives some nondipolar information in precordial tracings modified by proximity effect.[5] Proximity effects are of much more concern in children than in adults because the heart is much closer to the anterior chest wall over a wider area even without pathologic cardiac enlargement.[6] These proximity effects may exert a greater influence on the shape and amplitude of the T wave than on the QRS complex.[7] Isolated T wave inversion is an appelation given to isolated appearance of negativity of mean T wave potential in the midprecordium between adjacent positive T waves. Several reports on the subject have appeared since the detailed report of Grant and co-workers.[8] Most were based on observations in normal young adults,[9-11] whereas the phenomenon is most often found in atrial septal defect (ASD).[12,13] Incidence and mechanism in normal children and in children with other congenital heart anomalies, however, have been less well examined.

It is the purpose of this paper to explore the entire precordial T wave mean potential distribution and determination of the null line in relation to isolated T-wave inversion in precordial leads in childhood. The term null line refers to the isoelectric line dividing the positive and negative mean T wave potential fields.

Materials and methods

The study included 2,754 normal children and 274 patients with congenital heart

From the Department of Pediatrics, University of T[illegible] School of Medicine, Tokyo, Japan, and UCLA School of Medicine, Los Angeles, Calif.
Supported in part by Los Angeles County Heart Association.
Received for publication June 7, 1970.
Reprint requests to: Leonard M. Linde, M.D., Department of Pediatrics, UCLA School of [illegible], Calif. 90024.

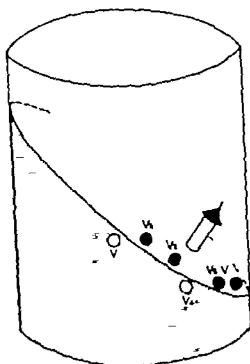


Fig. 1 A schematic representation of Grant model of mean T vector and null line. Dotted area shows the negative field of T wave potential. V is placed in the negative field.

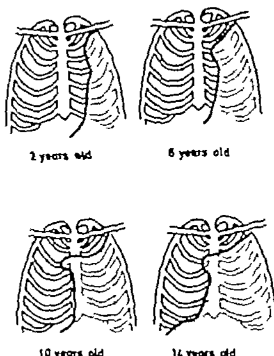


Fig. 2. A schematic illustration of experimentally obtained null line of normal children. The lower part of an S-shaped null line shifts to the right with increasing age.

the adult type T-wave pattern. In normal children only one crossing was elicited between the null line and the band along which the precordial electrodes were properly located. Isolated T-wave inversion was encountered in those whose leftward concavity was relatively marked so that V or V was placed in the negative potential area and precordial electrodes traversed the null line three times instead of once (Fig 3) However the rightward convexity and leftward concavity were always such that only one transition from negative to positive mean T wave potential was observed at a given horizontal level. No insular area of negative mean T wave potential was found surrounded completely by a positive potential field.

The effect of deep inspiration is displayed in Fig 4. Deep inspiration made the T wave taken 1 cm to the right of or along the null line, positive without any significant change in the corresponding configuration of the QRS complex at any

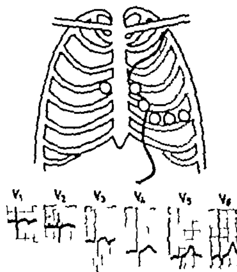


Fig. 3 An example of isolated T-wave inversion in normal child. V is located in the negative field.

Table I Incidence of isolated I wave inversion in normal children

Age (yr)	Total No for age	I T I	Per centage	The lead of negative T wave						Negative T_{II} and T_{III}
				I	I and I	I-I	I	I and I	V	
1	212	2 (1)†	0 96	?	0	0	0	0	0	0
2	161	3 (2)	1 89	2	1	0	0	0	0	0
3	157	1 (0)	0 95	0	1	0	0	0	0	0
4	00	2 ( )	1 00	2	0	0	0	0	0	0
5	213	3 (2)	1 41	2	1	0	0	0	0	0
6	253	5 (2)	2 00	4	2	0	0	0	0	0
7	222	0 (0)	0 00	0	0	0	0	0	0	0
8	200	2 (1)	1 00	2	0	0	0	0	0	0
9	212	2 (0)	0 91	1	2	0	0	0	0	0
10	183	0 (0)	0 00	0	0	0	0	0	0	0
11	192	1 (1)	0 5	1	0	0	0	0	0	0
12	172	4 (3)	? 32	4	0	0	0	0	0	0
13	152	3 (2)	1 98	3	0	0	0	0	0	0
14	125	0 (0)	0 00	0	0	0	0	0	0	0
15	110	0 (0)	0 00	0	0	0	0	0	0	0
Total	2 751	28 (16)	1 02	23	5	0	0	0	0	0

I T I = Isolated T wave inversion.
†( ) = male patient only

Table II Incidence of isolated T wave inversion in congenital heart disease in childhood

Defect	Total N	I T I	Per centage	The lead of negative T wave						Negative T_{II} and T_{aF}
				I	I and I	I-I	I	I and I	I	
ASD or its hemodynamic equivalents	67	36	53 7	0	6	0	15	8	7	1
VSD	68	17	25 0	3	2	0	7	4	1	0
PDA	46	10	27 1	3	1	0	5	1	0	0
Tetralogy of Fallot	35	3	8 6	0	0	0	2	0	1	0
Pulmonic stenosis with intact ventricular septum	8	1	12 5	1	0	0	0	0	0	0

potential of the T wave or the ST T complex was not as straight as in Grant's model (Fig 1) Generally two main curves were elicited resembling an S shape starting near the left axilla proceeding obliquely down to the right costal margin with a rightward convexity over the base and a lower leftward concavity (Fig 2) The concavity runs near V_3 and V_4 of normal children Individual differences were of degree of both convexity and concavity The null line moved as a whole from left to right with increase in age in accordance with the change from the juvenile to

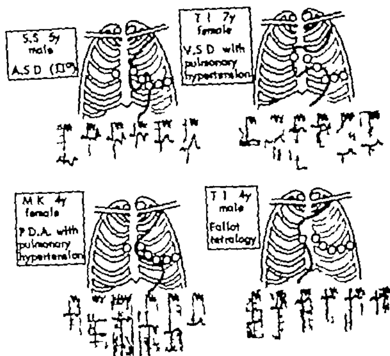


Fig 5 Typical examples of marked distortion of null line observed in congenital heart defects, and its relation t isolated T-wave inversion.

Discussion

Isolated T-wave inversion over the precordium has been attributed to several factors in young adults. Grant classified them into three main categories simulated isolated T wave negativity isolated T negativity syndrome and something resembling isolated T negativity [17]

In simulated isolated T-wave negativity the mean T wave vector is leftward oriented almost straightly superiorly and slightly anteriorly with resultant negative T_1 and T and a straight null line running from the right superiorly down to the left. Such a superiorly directed T vector was not observed in normal individuals Only one case of ASD manifested a negative T_1 and T at the same time but failed to reveal isolated T-wave inversion. It seems quite inaccurate to presume existence of such a model as displayed in Fig 1 in childhood in the discussion of the mean T wave potential, irrespective of the presence or absence of isolated T wave inversion

On the contrary the null line has a curved S shape subject to the distortion by the underlying cardiac enlargement and giving rise to isolated T wave inversion The present study indicates that simulated T wave negativity must be extremely rare if not nonexistent in the pediatric age group.

The interpretation of isolated T-wave negativity is based on several observations. The first is the presence of an isolated small area of negative T wave over the direct epicardium ascertained by Barbato and associates.[1] The second is the presence of the cardiac notch and the locations of V and V_4. The anterior surface of the right ventricular free wall is closest to the chest wall over the midprecordium. Sudden disappearance of the isolated T-wave inversion with deep inspiration is interpreted by some investigators as evidence that an isolatedly localized area of negative T wave over the midprecordium exists but disappears because expansion and aeration of the lung eliminate the influence of proximity effect, even though a total exploration of the precordium has not been

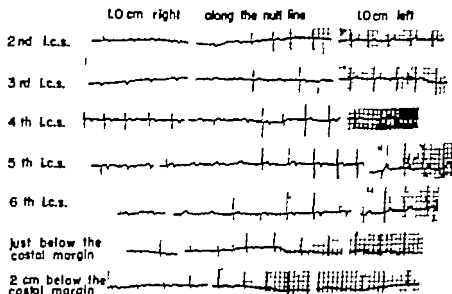


Fig. 4. Variable T wave potential with deep inspiration in relation to the null line. The ECG taken along the null line reveals a variable T wave: positive T wave with deep held inspiration and gradual negativization with deep expiration. The positive T wave resembles that taken 1.0 cm left of the null line, while the negative T wave 1.0 cm right.

horizontal level. The phase of the T wave recorded at the null line changed with deep breathing. The shape of the negative T wave in full expiration closely resembled that taken 1 cm to the right of the null line while the configuration of the positive T wave in deep inspiration resembled that taken 1 cm to the left. Change of configuration with respiration was most marked at the fourth to sixth intercostal spaces. If the negative T_{V_3} and or T_{V_4} were located just a short distance right of the null line deep inspiration made them positive as if an isolated insular area of T wave inversion was really present in the midprecordium and V_3 or V_4 were placed in the midst of the negative field and it looks as if the maneuver made V_3 or V_4 distant enough from the heart to be significantly free of proximity effect with the resultant disappearance of the isolated negative T wave insular area.

Congenital cardiac anomalies disclosed qualitatively and quantitatively different maps in accordance with the underlying hemodynamics and different types of cardiac enlargement. Left ventricular enlargement did not generally distort the ordinary map of the null line over the anterior precordium whereas right ventricular enlargement often did. The null line of TF usually had a rightward displaced figure for age especially in the lower part of the curve. The ordinary smooth S shape was still preserved and the degree of displacement depended upon the severity of the disease. Exaggeration of an ordinary S-shaped contour was observed in ASD in which right ventricular enlargement was a prominent feature and a mild rightward protrusion of the upper convexity with a marked lower leftward concavity of the curve was seen. The leftward concavity was so exaggerated in some cases that the null line was not only concave to the left but was distorted upward as illustrated in Fig. 5. This type of distortion provided a situation for the occurrence of isolated T wave inversion over the midprecordium. Isolated T wave inversion in PDA and VSD was not infrequently associated with pulmonary hypertension and marked right ventricular enlargement. The null line in these cases was considerably distorted as in ASD. The rightward displacement of the upper part however was more marked in these cases compared to ASD corresponding to the positive T_{V_1} criterion of right ventricular hypertrophy. For mean T wave potential there was always one null line over the precordium whether cardiac enlargement was present or not.

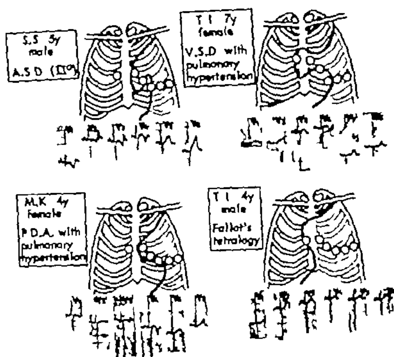


Fig. 5 Typical examples of marked distortion of null line observed in congenital heart defects, and its relation to isolated T-wave inversion.

Discussion

Isolated T-wave inversion over the precordium has been attributed to several factors in young adults. Grant classified them into three main categories: simulated isolated T wave negativity, isolated T negativity syndrome and something resembling isolated T negativity.[17]

In simulated isolated T wave negativity the mean T wave vector is leftward oriented almost straightly superiorly and slightly anteriorly with resultant negative T_I and T_{VF} and a straight null line running from the right superiorly down to the left. Such a superiorly directed T vector was not observed in normal individuals. Only one case of ASD manifested a negative T_I and T_{VF} at the same time but failed to reveal isolated T wave inversion. It seems quite inaccurate to presume existence of such a model as displayed in Fig. 1 in childhood in the discussion of the mean T-wave potential irrespective of the presence or absence of isolated T wave inversion.

On the contrary, the null line has a curved S shape subject to the distortion by the underlying cardiac enlargement and giving rise to isolated T wave inversion. The present study indicates that simulated T-wave negativity must be extremely rare if not nonexistent in the pediatric age group.

The interpretation of isolated T wave negativity is based on several observations. The first is the presence of an isolated small area of negative T wave over the direct epicardium ascertained by Barbato and associates. The second is the presence of the cardiac notch and the locations of V_3 and V_4. The anterior surface of the right ventricular free wall is closest to the chest wall over the midprecordium. Sudden disappearance of the isolated T wave inversion with deep inspiration is interpreted by some investigators as evidence that an isolatedly localized area of negative T wave over the midprecordium exists but disappears because expansion and aeration of the lung eliminate the influence of proximity effect, even though a total exploration of the precordium has not been

done and the presence of a localized inverted T wave area is not confirmed The present investigation disclosed a peculiarly shaped but consistent null line dependent on age the underlying hemodynamics and the resultant ventricular enlargement Isolated T wave inversion results from exaggerated distortion of the null line The mean T wave potential changed with deep inspiration in every case at any horizontal level near or along the null line as a result of its apparent rightward shift independent of the presence or absence of isolated T wave inversion This is thought to be brought about by the relative postural change of the heart in relation to the anterior chest wall A marked sudden change of configuration and potential over the fourth to sixth intercostal spaces along the null line seems to result from a relatively significant postural change in anatomic relation to the exploring electrode Therefore the sudden disappearance of a negative T wave with deep inspiration does not in itself confirm the presence of localized negative T area in the midst of a positive field If the isolated negative T lead is located far to the right of the null line deep inspiration can hardly produce enough shift of the null line to invert the T wave potential of the lead

Proximity effect is particularly important in right ventricular enlargement in view of the distortion of the null line

Summary

Isolated T wave inversion in the pediatric precordial electrocardiogram was studied with respect to incidence and underlying mechanisms.

Total precordial T wave mean potential distribution was explored in normal controls and in patients with a variety of congenital cardiac diseases Simulated isolated T wave negativity as described by Grant, was not found in the present study nor were localized precordial negative T islands surrounded by positive T areas. An S-shaped null line a dividing line between positive and negative fields for the T wave, was observed in all cases under study Its configuration varied with age and enlargement of the heart, especially of the right ventricle Abnormality in its configuration varied with age and enlargement of the heart especially of the right ventricle. Abnormality in its configuration gave rise to the occurrence of isolated T wave inversion Deep inspiration brought about the positivization and apparent rightward shift of the T wave potential map in every case at any horizontal level along the null line. It was confirmed that the maneuver by itself did not provide the basis for the presence of a circumscribed isolated negative T wave area over the midprecordium

The authors wish to express their profound gratitude to Professor Tadao Takatsu for his critical review and support. We are much indebted to Dr Kenichi Harumi for his valuable advice. We are also very grateful for the technical assistance given by Mrs. Yuko Sakamoto.

REFERENCES

1 Fischman, E. J and Elliot B J Experimental comparison of "parallel grid leads with simple bipolar and the SVEC III Frank and McFee-Parungao systems. I Sagittal leads, AMER HEART J 6 792 1964
2. Fischman, E. J Experimental comparison o parallel grid leads with simple bipolar an the SVEC III Frank and McFee-Parungao systems II Transverse and vertical leads AMER. HEART J 70:627 1965.
3 Ellison, R. C., Fischman, E. J Miettinen O S. and Hugenholtz P G Use of the dipole moment in the assessment of left ventricular hypertrophy Circulation 40 719 1969
4 Barber M R. and Fischman, E. J A lead system recording total outward cardiac dipole strength Brit Heart J 23:649 1961.
5 Taccardi, B Distribution of heart potentials on the thoracic surface of normal human subjects, Circ. Res. 12:34 1963.
6. Spach M S. Silverberg W P Boineau, J P Barr R. C Long E. C. Gallie T M Gabor J B and Wallace, A. G. Body surface isopotential maps in normal children, ages four to 14 years, AMER. HEART J 72:640, 1967
7 Awa, S. Linde, L. M Oshima M Okuni, M Momma, K and Nakamura N The significance of late-phased dart T wave in the electrocardiogram of children. (to be published)
8 Grant, R. P Estes, E. H and Doyle, J T Spatial vectorelectrocardiography The clinical characteristics of the S-T and T vectors, Circulation 3:182 1951
9 Wasserburger R. H. and Loven, T H The effect of hyperventilation and probanthine on isolated R S-T segment and T wave abnormalities, AMER. HEART J 51:666, 1956.
10. Littman D Abnormal electrocardiograms in the absence of demonstrable heart disease, Amer J Med. 5:337 1948.
11 Goldman M J : Normal varia[illegible] in the elec-

trocardiogram leading to cardiac invalidism, Amer. Heart J. 59:71 1960.

12. Wasserburger R. H., Siebecker K. L., Jr and Lewis, W. C., The effect of hyperventilation on the normal adult electrocardiogram, Circulation 13:850, 1956.
13. Pruitt, R. D. Klakeg, C. H., and Chapin, LeE. Certain clinical states and pathological changes associated with deeply inverted T waves in the precordial electrocardiogram, Circulation 11:517 1955
14. Schlatt, R. C., Levine, H. D. and Bailey C. C.: Isolated T wave negativity in the ischemic phase of myocardial infarction in man, Circulation 10:829 1954.
15. Toscano-Barboza, E., Brandenburg, R. O., and Swan, H. J. C. Atrial septal defect. The electrocardiogram and its hemodynamic correlation in 100 proved cases, Amer. J. Cardiol 2:698, 1958.
16. Takatsu, T. and Okuni, M., A guide to pediatric electrocardiography Tokyo, Japan, 1964 Shindan Chiryosha Co., Ltd.
17. Grant, R. P. Clinical electrocardiography New York, 1957 McGraw Hill Book Company Inc.
18. Barbato, E. Debes, A. C., F Fiola, T Pileggi, F Zerbini, E. J. and Decourt, L. V.: Direct epicardial and thoracic lead. Their relationship in man, Amer. Heart J. 58:238, 1959
19. Blackman, N. S. and Kuskin, L.: Inverted T waves in the precordial electrocardiogram of normal adolescent Amer. Heart J. 6 301 1961

T-wave abnormalities during hyperventilation and isoproterenol infusion

*Leonard Biberman, M.D.**
*R. N. Sarma, M.D.***
*Borys Surawicz, M.D.****
Lexington, Ky.

Hyperventilation (HV) may produce abnormally low or inverted T waves in the electrocardiogram (ECG) of healthy persons without heart disease.[1] The cause of these T-wave abnormalities remains uncertain. Some of the contributing factors considered by various investigators include respiratory alkalosis,[4-10] change in extracellular K concentration,[10] change in heart position,[11,12] tachycardia,[2] and vagally mediated reflex.[1]

Yu and co-workers[1] showed that the T-wave abnormalities occurred during HV with room air but not during HV with 6 per cent CO_2. This observation suggested that the abnormalities could be due to alkalosis, but the mechanism by which alkalosis contributed to the development of such T-wave abnormalities was not obvious. In the subjects studied by Yu and co-workers the heart rate was more rapid during HV with room air than with 6 per cent CO_2. This suggested the possible role of tachycardia, but the same study showed that tachycardia induced by exercise did not produce T-wave abnormalities.[1] The effect of alkalosis in the absence of tachycardia has not been studied.

Yu and co-workers have shown that the T-wave abnormalities produced by HV were similar to the abnormalities produced by intravenous administration of 20 μg of epinephrine. Recent studies have shown that the T-wave abnormalities produced by HV can be prevented by pretreatment with propranolol.[1,13] These reports suggest that beta-adrenergic stimulation may contribute to the production of these abnormalities. It appears, therefore, that an understanding of the T-wave changes produced by HV requires an understanding of the effect of beta-adrenergic stimulation on ventricular repolarization.

The purpose of the present study was to (1) re-evaluate the role of the several factors which have been previously implicated in the pathogenesis of the T-wave abnormalities induced by hyperventilation, (2) study the ECG effects of respiratory alkalosis in the absence of tachycardia

From the Cardiovascular Division, Department of Medicine, University of Kentucky College of Medicine, Lexington, Ky.

Supported by National Institutes of Health Research Grant HE 07390 and by National Institutes of Health Training Grant HE 05598.

Received for publication April 7, 1970.

Reprint requests to: Dr. Borys Surawicz, University of Kentucky College of Medicine, Department of Medicine, Lexington, Ky. 40506.

*United States Public Health Service Research Fellow (HT 35631).

**Research Associate.

***Professor of Medicine, Director of Cardiovascular Division.

and (3) study the effects of isoproterenol on the ECG of persons with T wave abnormalities induced by hyperventilation

Material

In our laboratory the effect of hyperventilation on the ECG is tested routinely in all patients subjected to an exercise test. We studied six male and six female ambulatory patients in whom T-wave abnormalities had been observed after hyperventilation. The age of these patients ranged from 19 to 1 years. None of these patients had evidence of heart disease and all had normal chest roentgenograms. We also studied eleven healthy students ten male and one female, selected at random Their ages ranged from 17 to 7 years.

All the students and ten of the patients had normal ECG's at rest while two patients had slight nonspecific T-wave abnormalities at rest None of the students or patients had chest pain depression of the S-T segment or inversion of previously upright T wave during or after a three minute Master two-step exercise test

Methods

All studies were performed about two hours postprandially Following a 30 minute period of rest in the supine position an ECG was recorded in the midrespiratory maximal inspiratory and maximal expiratory positions with the subjects supine and in the midrespiratory position after 30 to 60 seconds of standing The six standard limb leads and subsequently six precordial leads (V_{1-6}) were simultaneously recorded with a six channel direct writing recorder at a paper speed of 25 or 50 mm. per second ECG's were also continuously recorded during the following three types of hyperventilation i the supine position (1) The first type was rapid open hyperventilation (ROHV) during which the subjects breathed room air as rapidly and deeply as possible Two subjects hyperventilated for 30 seconds and 21 for 60 seconds. (2) The second type was rapid closed hyperventilation (CHV) during which the subject rebreathed air as deeply and as rapidly as possible from a respirometer The purpose of this procedure was to prevent alkalosis. Six subjects hyperventilated for 30 seconds and 17 for 60 seconds. (3) The third type was slow open hyperventilation (SOHV) during which the subjects breathed room air as deeply as possible at a respiratory rate adjusted to maintain the heart rate below 90/minute The respiratory rate varied from 15 to 25 breaths per minut

A Riley needle was inserted into the brachial artery for blood sampling The samples were drawn before the first HV procedure and immediately after each of the subsequent HV procedures. In 8 subjects blood samples were obtained after all three types of HV and in 14 only after rapid open and closed hyperventilation (ROHV and CHV) Plasma sodium and potassium concentration were determined with a flame photometer plasma Ca concentration by EDTA titration using a calcein indicator and plasma Mg with an atomic absorption spectrophotometer† Blood pH pO_2 and pCO_2 were measured with microelectrodes‡ calibrated before each measurement. The accuracy of the blood gas measurements was determined by tonometry Th pO measurements were accurate within 2 mm Hg and the pCO_2 measurements within 1 mm Hg

In eleven subjects (9 patients and 2 students) in whom after ROHV an initially positive T wave became inverted in one or more of Leads I II V_{3-6} a solution containing µg per milliliter isoproterenol in 5 per cent aqueous dextrose was infused intravenously 20 to 30 minutes after the last HV procedure The infusion was administered at a rate of 3 to 6 µg isoproterenol per minute for 4 to 6 minutes. The ECG was recorded continuously during the infusion in the same manner as during HV

The Q-T interval was measured by the method previously described[11] and the Q-T interval was calculated by the formula

$$Q\text{-}T = \frac{Q\text{-}T}{\sqrt{R\ R}}$$

The R R and Q-T intervals and T wave amplitude were deter

*Isuprel.
†Techtron AA-3.
‡Instrumentation Laboratory pH-Gas Analyzer.

mined by averaging the values measured in the cycle with a maximum T change and the four subsequent cycles

The t test was used to evaluate the significance of the differences between the paired variables The association between two different measurements was evaluated by product moment correlation coefficients A p value less than 0 05 was considered significant

Results

Leads II and V_4 were selected for statistical evaluation of the T wave and Q T changes Changes in these two representative leads were similar to changes in other leads.

Effect of position and HV on the T wave Table I shows the mean value and standard deviation of the T wave amplitude in the midrespiratory position after inspiration expiration standing and during rapid open and closed hyperventilation in 23 subjects There was no significant change in T wave amplitude in either lead after expiration or in Lead V after inspiration The T wave amplitude in Lead II decreased after inspiration but this decrease was significantly less than the decrease produced by the upright position CHV and ROHV The decrease of the T wave amplitudes produced by ROHV was significantly greater than the decrease produced by the upright position and CHV

Inversion of a previously upright T wave in one or more of Leads I II V_{2-4} occurred only after ROHV and CHV After ROHV the T wave became inverted in eight of eleven students and in all of the patients and after CHV in two students and in six patients.

The onset and the duration of the T wave abnormalities varied in different individuals. The greatest decrease in the amplitude or the deepest inversion of the T wave occurred after 15 to 40 seconds of either ROHV or CHV We conclude that the T wave abnormalities produced by ROHV and CHV could not be due to changes in heart position

Effect of three different types of HV on arterial blood gases and plasma electrolyte concentration Table II shows the mean values and standard deviation of the plasma electrolyte concentrations blood pH pO_2 and pCO_2 after CHV and ROHV in 14 subjects (5 students and 9 patients) and after SOHV in eight of these 14 subjects (2 students and 6 patients) The average T-wave amplitude before HV after CHV and after ROHV in these 14 subjects was not significantly different from the average T wave amplitude of the total sample of 23 subjects included in Table I

CHV produced no significant change in pH or pCO_2 while both ROHV and SOHV produced significant increases in pH and significant decreases in pCO_2 The difference between the pCO_2 after ROHV and SOHV was not significant but the pH was significantly higher after SOHV than after ROHV The pO_2 increased after all types of HV After ROHV there was a small but

Table I Amplitude of T wave during inspiration expiration in the upright position and after hyperventilation in 23 subjects

T amplitude in 0.1 mv	Recumbent	Maximal inspiration recumbent	Maximal expiration recumbent	Upright	Hyperventilation rebreathing expired air (CHV)	Hyperventilation room air (ROHV)
Lead II	2 6 ±1 4	1 7 ±1 6	2 5 ±1 4	1 1 ±1 3	0 8 ±1 5	−0 1 ±1 5
Lead V_4	4 3 ±2 4	4 0 ±2 1	3 9 ±2 4	2 9 ±2 2	2 7 ±2 4	0 8 ±2 5

In this table and in Table II, the T-wave amplitude after hyperventilation represents the lowest upright or the deepest inverted T wave recorded during or after hyperventilation. See text.

statistically significant rise in plasma potassium concentration Other procedures did not significantly alter plasma K and none of the procedures produced significant changes in plasma calcium magnesium and sodium concentrations.

Effect of three different types of HV on the ECG Slow open hyperventilation produced no significant change in T wave amplitude in either Lead II or V_4 (Table II) Heart rate increased after all three types of hyperventilation and the R R interval after all types of HV was significantly different from each other as well as from the control. The Q-T interval did not change significantly after SOHV but increased significantly after both CHV and ROHV The mean Q-T interval was slightly longer after ROHV than after CHV but this difference was not significant.

Table II shows that the greatest T wave abnormality occurred after ROHV and was accompanied by a significant decrease in pCO_2, increase in pH shortening of the R R interval, and prolongation of the Q-T interval. The product-moment correlations between the changes in the T wave amplitude and the changes in blood pH and pCO were not significant, but the change of the T wave amplitude correlated significantly with the decrease of the R R interval and the increase of the Q-T interval The T-wave abnormalities during HV could not be attributed exclusively to a critical shortening of the R R interval since we recorded in each subject one or more ventricular complexes in which the R R interval was the same but the T wave was normal or less abnormal than the most abnormal T wave during HV These complexes were recorded after longer periods of HV during recovery from HV or after exercise. In all 23 subjects the ventricular complex with the more abnormal T wave during HV was associated with a longer Q-T interval than the ventricular complex with the less abnormal T wave but the same R R interval (Figs. 1 and)

Effect of ISP on the ECG The effects of isoproterenol (ISP) infusion have been divided into early and late and the results are shown in Table III and in Figs. 3 and 4 During the early phase of the infusion the T wave amplitude decreased in all subjects and the previously upright T wave became negative in one or more of Leads I II or V_4 in ten of eleven subjects. The maximal T wave inversion usually occurred 30 to 40 seconds after beginning the ISP infusion and was associated with a signifi

Table II Effect of three different types of hyperventilation on the arterial blood gases plasma electrolyte concentration, and electrocardiogram

Procedure	N of subjects	pH units	pCO_2 mm. Hg	pO_2 mm Hg	K mEq/L	Ca mEq/L	Mg mEq/L	T amplitude in 0.1 mv: Lead II	T amplitude in 0.1 mv: Lead V	R-R in 0.01 sec.	Q-T
Control	14	7.43 ±0.02	38.7 ±2.1	77.6 ±6.4	4.02 ±0.40	5.00 ±0.27	1.65 ±0.16	2.82 ±1.40	2.94 ±2.10	80 ±11	41 ±01
Rapid HV rebreathing (CHV)	14	7.42 ±0.01	33.6 ±3.1	86.9 ±8.9	4.60 ±0.43	5.03 ±0.35	1.69 ±0.11	0.51 ±1.52	2.31 ±2.08	65 ±08	41 ±03
Rapid HV room air (ROHV)	14	7.58 ±0.06	24.6 ±4.6	95.7 ±8.0	4.93 ±0.42	5.29 ±0.30	1.67 ±0.15	−0.52 ±1.36	0.32 ±2.48	47 ±05	45 ±03
Slow HV room air (SOHV)	8	7.61 ±0.06	16.5 ±4.1	103.6 ±12.3	4.50 ±0.27	4.95 ±0.23	1.61 ±0.17	1.94 ±1.74	4.36 ±3.46	69 ±12	39 ±03

See text.

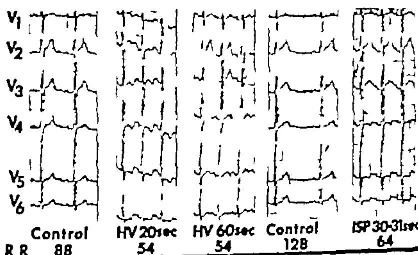


Fig. 1. Simultaneously recorded ECG Leads V[illegible] (paper speed 25 mm. per second) in a 23-year-old student. Control: R R = 88, Q-T = 39, Q-T = 40. After 20 second ROHV: R R = 54, Q-T = 35, Q-T = 48. After 60 second ROHV: R R = 54, Q-T = 30, Q-T = 41. Note that the R R interval after 20 and 60 seconds of HV is the same but after 20 seconds of HV the T wave is negative and the Q-T interval is longer. ISP infusion at a rate of 4 μg per minute: R R = 64, Q-T = 42, Q-T = 52. Note that the T and Q-T changes after ISP and after 20 seconds HV are similar. All intervals in this and in the subsequent legends are expressed in 0.01 sec.

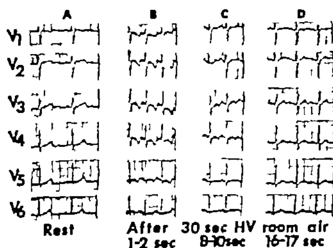


Fig. 2. Simultaneously recorded ECG Leads V[illegible] (paper speed 25 mm. per second) in a 21-year-old student. *A*, Control before HV: R R = 85, Q-T = 39, Q-T = 41. *B*, During first 2 seconds after 30 seconds ROHV: R R = 44, Q-T = 32, Q-T = 48. *C*, During eighth and tenth second: R R = 44, Q-T = 30, Q-T = 45. *D*, During sixteenth to seventeenth second: R R = 56, Q-T = 32, Q-T = 43. Note that the R R intervals in *B* and *C* are the same but in *C* the Q-T and Q-T intervals are shorter and the T waves less inverted.

cant lengthening of the Q-T interval. Subsequently, the T wave became more upright, the Q-T interval decreased, and U wave amplitude increased. Table III shows that after approximately two min-

utes of ISP infusion the T wave amplitude in Lead V[illegible] and the Q-T interval were not significantly different from the control, but in some cases the T waves in certain leads were taller than before the ISP infusion (Leads V[illegible] in Fig. 3). Table III and Fig. 4 show that the initial decrease of T wave amplitude was associated with an increased heart rate without an appreciable change in Q-T interval. As a result, the Q-T interval was increased. The subsequent increase of T wave amplitude was associated with a significant decrease in Q-T and Q-T intervals and a slight insignificant decrease in the R R interval. In the same subjects the T wave inversion during hyperventilation and the isoproterenol infusion was associated with similar increases in the Q-T interval (Fig. 1).

Discussion

It has been reported that T wave inversion occurs after HV in about 10 per cent of healthy persons.[1,2] In our study HV produced T wave inversion in at least one of several simultaneously recorded ECG leads in eight of eleven or 73 per cent of randomly selected healthy students. In some of our subjects T wave abnormalities were more pronounced during HV than immediately after 60 seconds

Table III Effect of isoproterenol (ISP) on the ECG in Lead V

Subject No.	Rate of I.P. infusion μg/min.	Control T	Control R-R	Control Q-T	Control Q-T	Early ISP effect Time sec	Early T	Early R-R	Early Q-T	Early Q-T	Late ISP effect Time sec	Late T	Late R-R	Late Q-T	Late Q-T
		0.1 mv in 0.01 sec					0.1 mv in 0.01 sec					0.1	in 0.01 sec		
1	6.0	2.0	54	30	41	43	−1.0	44	30	45	160	1.5	41	28	37
2	4.0	3.0	80	35	43	30	−1.0	62	34	49	150	4.0	61	32	39
3	4.0	6.0	77	36	41	50	−0.5	58	34	47	291	3.0	35	30	40
4	3.0	2.0	78	42	36	46	−1.0	59	32	49	230	2.0	6?	?5	35
5	3.0	0.5	73	30	42	30	− 6	56	30	45	236	1.0	41	?	40
6A	4.0	4.5	76	34	40	35	1.0	54	31	43	174	4.3	49	29	41
6B	6.0	4.0	72	33	39	33	0.5	54	33	43	32	4.5	55	30	49
7	4.0	−1.5	72	31	42	43	−3.0	62	34	41	103	6.0	41	29	42
8	3.5	5.0	100	38	37	30	±0.5	82	38	48	50	4.0	55	31	43
9	3.0	3.0	85	35	40	40	−1.0	63	28	44	170	0	64	33	41
10A	4.0	10.0	90	39	42	60	2.0	74	35	4	1.0	15.0	71	34	40
10B	6.0	8.0	88	30	40	50	2.0	57	29	43	?3	7.0	61	31	40
11	4.0	2.5	72	36	40	40	−0.5	42	32	44	134	3.0	49	?5	41
Mean		3.7	73	33	40.4	37.3	0.27	60.2	31.5	44.1	147	4.5	56.2	31.5	40.6
S.D.		±2.3	±11	±3.1	±1.7	±9.4	±1.5	±7.6	±2.1	±2.3	±34	±3.6	±10.1	±2.0	±1.5

The early ISP effect designates the time of the maximal decrease of T-wave amplitude or maximal T-wave inversion. The late ISP effect designates the time of the maximal upright T wave. The − sign in front of the T wave designates negative and the ± sign, diphasic T wave. See text.

of HV (Fig. 2). Similar observations were reported by Lewis[9] and Crede and coworkers.[10] It appears, therefore, that the true incidence of T-wave abnormalities during HV may be underestimated unless multiple ECG leads are monitored during the HV.

T-wave abnormalities induced by HV were attributed to a change in heart position by Scherf and associates[11,12] but not by other investigators.[4,14,7] Our study showed that the T-wave changes associated with ROHV were significantly greater than the T-wave changes produced by standing or by maximal inspiration and expiration in the supine position.

Some investigators attributed T-wave changes after HV to alkalosis[1] or to the rapidity of the fall in pCO_2. In our study the T-wave abnormalities after HV were not related to alkalosis. During CHV T-wave inversion occurred without change in blood pH. The correlation between the T-wave changes and the increase in blood pH during ROHV was not significant while SOHV produced more severe alkalosis than ROHV but did not alter the T-wave amplitude. The latter observation is in agreement with the observation of Scherf and co-workers[12] who found only minimal T-wave abnormalities and no T-wave inversion after the slow deep hyperventilation carried out until the onset of tetany. However, blood pH was not measured in Scherf's experiments.

Several studies have shown a transient rise in plasma K (Kp) concentration during the early stages of HV[14-20] and a decrease in plasma K after longer HV.[20-22] We found a slight rise in Kp after ROHV but no fall in Kp after six minutes of SOHV. The small rise in Kp which occurred in our subjects after ROHV would not explain the T-wave inversion and the Q-T lengthening.[4]

In our subjects the heart rate was more rapid after ROHV than after CHV. This is in agreement with the results of other studies in which the heart rate was more rapid during HV with room air than after

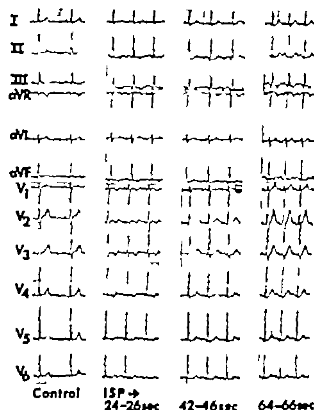


Fig. 3. Simultaneously recorded Leads I aV and V (paper speed 25 mm. per second) in a 3 year-old man without heart disease during ISI infusion at rate of 3.5 μg per minute. Control R R = 92 Q-T = 37 Q-T = 39 When T wave becomes negative in Lead II and V (24 to 26 seconds) R R = 6 Q-T = 37 Q-T = 47 When T wave becomes upright (42 to 46 second) R R = 55 Q-T = 34 Q-T = 44 When T wave amplitude increases (64 to 66 second) R R = 52 Q-T = 31 Q-T = 43 Note that the T wave inversion in Leads II aVF and V associated with the longest Q-T.

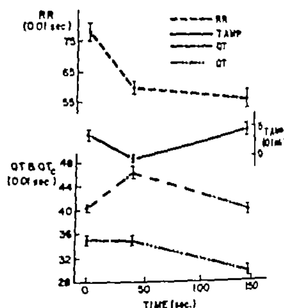


Fig. 4. Diagrammatic representation of selected data from Table III. Each point designates the mean value and the vertical bar the standard error. Note that Table III presents standard deviation and not the standard error. See text.

rebreathing the expired air or hyperventilating with air containing 6 per cent CO_2.[8,10] These findings suggest that the respiratory alkalosis produced by HV contributes to the increase in heart rate.

Our study shows that the T wave abnormalities produced by HV were accompanied by tachycardia but could not be attributed solely to a critical increase in heart rate. This conclusion is in agreement with previous studies in which the T wave became inverted after HV but remained upright when tachycardia was induced by exercise[3,10] intravenous administration of propantheline[10] or breathing air containing 5 per cent CO_2.[8,4]

Infusion of isoproterenol produced transient T wave inversion in one or more of Leads I II V in ten of eleven subjects without heart disease. Similar effects of isoproterenol infusion in cats have been observed by Raab and Lepeschkin.[17] The transient T wave inversion which occurred during isoproterenol infusion was similar to the transient T wave abnormalities produced by HV. Both were associated with an increase in heart rate a prolonged Q T interval and hysteresis of the Q-T interval. The common mechanism underlying these changes could be an asynchronous shortening of ventricular repolarization during the early phase of isoproterenol infusion and during sympathetic stimulation produced by hyperventilation. The presence of such asynchronous shortening of repolarization in various areas of ventricular myocardium is supported by experimental studies of Han and associates[4] who have shown that both epinephrine infusion and left stellate ganglion stimulation cause an early increase in temporal dispersion of refractory periods in the dog ventricle. If one accepts the hypothesis that the T wave is normally upright because repolarization lasts longer in the subendocardial than in the subepicardial layers[18] then the transient T wave inversion during sympathetic stimulation or

ISP infusion may be attributed to an earlier shortening of repolarization in the subendocardial rather than in the subepicardial layers.

Summary

We studied the effects of three types of hyperventilation (HV) on the ECG, arterial blood gases, and plasma electrolyte concentration in twelve patients without heart disease in whom HV produced T wave abnormalities, and in eleven healthy volunteers. The T wave abnormalities produced by HV could not be attributed to alkalosis, changes in plasma Na, K, Ca, or Mg concentrations, or changes in heart position. In ten of eleven subjects in whom the T wave became inverted during HV, isoproterenol infusion at a rate of 3 to 6 μg per minute also produced T wave inversion. In all subjects the T wave inversion during HV and isoproterenol infusion was transient, occurred at the onset of tachycardia, and was associated with prolongation of the Q-T interval attributed to the hysteresis of the Q-T interval. We have postulated that the transient T wave abnormalities during HV and isoproterenol infusion may be due to asynchronous shortening of repolarization.

We wish to acknowledge the assistance of Dr. E. D. Ross with the electrolyte determinations, Dr. R. W. B. Penman in determinations of blood gases (laboratory supported by National Institutes of Health Grant HE 06932), and Dr. L. S. Gettes and Dr. R. Shabetai for their review of the manuscript.

REFERENCES

1. Wasserburger, R. H., Siebecker, K. L., Jr., and Lewis, W. C.: The effect of hyperventilation on the normal adult electrocardiogram, Circulation 13:850, 1956.
2. Salvetti, A., Celle, P. L., Arrigoni, P., and Buzzalana, D.: Comportamento della fase di ripolarizzazione ventricolare dopo sforzo, dopo iperventilazione volontaria in giovani sani, Cuore Circ. 48:192, 1964.
3. Kemp, G. L., and Ellestad, M. H.: The significance of hyperventilation and orthostatic changes in the ECG, A.M.A. Arch. Intern. Med. 121:518, 1968.
4. Barker, P. S., Schrader, E. L., and Ronzoni, E.: The effects of alkalosis and of acidosis upon the human electrocardiogram, Amer. Heart J. 17:169, 1939.
5. Christensen, B. C.: Variations in the carbon dioxide tension in the arterial blood and the electrocardiogram in man, Acta Physiol. Scand. 12:389, 1946.
6. Christensen, B. C.: Studies in hyperventilation. II. Electrocardiographic changes in normal man during voluntary hyperventilation, J. Clin. Invest. 25:880, 1946.
7. Thompson, W. P.: The electrocardiogram in the hyperventilation syndrome, Amer. Heart J. 25:372, 1943.
8. Briquemont, F.: Le syndrome d'hyperventilation, Acta Cardiol. (Brux.) 16:539, 1961.
9. Lewis, B. I.: Mechanism and management of hyperventilation syndromes, Biochem. Clinics 4:89, 1964.
10. Y. P. N. Yim, B. J. B., and Stanfield, C. A.: Hyperventilation syndrome, A.M.A. Arch. Intern. Med. 103:490, 1959.
11. Scherf, D., and Schlachman, M.: The electrocardiographic changes caused by hyperventilation, Amer. J. Med. Sci. 213:342, 1947.
12. Scherf, D., Yildiz, M., and Jody, A.: Electrocardiographic changes during hyperventilation tetany, Amer. J. Med. Sci. 236:369, 1958.
13. Furberg, C., and Tengblad, C. F.: Adrenergic beta receptor blockade and the effect of hyperventilation on the electrocardiogram, Scand. J. Clin. Lab. Invest. 18:467, 1966.
14. Pentimone, F., Pesola, A., L. Abbate, A., Smorfa, A., and Giusti, C.: Effetto del propranololo sulle modificazioni elettrocardiografiche secondarie alla prova da iperventilazione volontaria ed alla prova ortostatica, Cuore e Circ. 51:79, 1967.
15. Lepeschkin, E., and Surawicz, B.: The measurement of the Q-T interval of the electrocardiogram, Circulation 6:378, 1952.
16. Crede, R. H., Chivers, N. S., and Shapiro, A. P.: Electrocardiographic abnormalities associated with emotional disturbances, Psychosom. Med. 13:277, 1951.
17. Lepeschkin, E.: Modern electrocardiography, Baltimore, 1951, The Williams & Wilkins Company, p. 282.
18. Rapoport, S., Stevens, C. D., Engel, G. L., Ferris, E. B., and Logan, M.: The effect of voluntary overbreathing on the electrolyte equilibrium of arterial blood in man, J. Biol. Chem. 163:411, 1946.
19. Hickam, J. B., Wilson, W. P., and Frayser, R.: Observations on the early elevation of serum potassium during respiratory alkalosis, J. Clin. Invest. 35:601, 1956.
20. Bleas, S. B., Gonzales, N. C., and Cingolani, H. E.: Early increase in plasma potassium in hyperventilation, Amer. J. Physiol. 208:537, 1965.
21. Giebisch, G., Berger, L., and Pitts, R. F.: The extrarenal response to acute acid-base disturbances of respiratory origin, J. Clin. Invest. 34:231, 1955.
22. Elkinton, J. R., Singer, R. B., Barker, E. S., and Clark, J. K.: Effects in man of acute experimental respiratory alkalosis and acidosis on ionic transfers in the total body fluids, J. Clin. Invest. 34:1671, 1955.

23. Stanbury S W and Thompson A E The renal response to respiratory alkalosis Clin Sci 11:357 1952
24. Surawicz B Relationship between electrocardiogram and electrolytes Amer Heart J 3:811 1967
25. George W K George W D Jr Smith J J Gordon F I Baird F E and Mills C C Changes in serum calcium serum phosphate and red-cell phosphate during hyperventilation New Eng J Med 270:7 6 1964
26. Lincoln A and Rose C A The ionized complexed and protein-bound fraction of calcium in plasma Quart J Med 100:60 1958
27. Raab, W and Lepeschkin, L Cardiac effects of N alkyl homologues of epinephrine (N-isopropyl and N-ethyl-epinephrine) Cardiologia (Basel) 16:332 1950.
28. Han J Garcia de Jalon P and Moe G K Adrenergic effect on ventricular vulnerability Circ Res 14:516, 1964
29. Grant R I Clinical electrocardiography New York 1957 McGraw Hill Book Company Inc p. 69

Pulmonary angiography in acute pulmonary embolism: indications, techniques, and results in 367 patients

James E. Dalen, M.D.
Harold L. Brooks, M.D.
Lewis W. Johnson, M.D.
Steven G. Meister, M.D.
Merrill M. Szucs, Jr., M.D.
Lewis Dexter, M.D.
Boston, Mass.

Although angiographic techniques were first used to visualize the pulmonary vasculature more than 30 years ago,[1,2] this technique has been adapted to the detection of acute pulmonary embolism in man only in the past few years.

The first angiographic studies relating to pulmonary embolism in man were reported in patients being evaluated for primary pulmonary hypertension and/or cor pulmonale of unknown cause.[3,4] In these studies, contrast medium was injected into the superior vena cava, and various angiographic abnormalities consistent with pulmonary vascular disease and or recurrent pulmonary embolism were noted.

The first large series of patients to be studied by angiography because of suspected acute pulmonary embolism was reported by Williams and Wilcox[5] in 1963. Sasahara and associates[6] and Alexander and co-workers[7] were the first to report the use of selective pulmonary angiography in the detection of acute pulmonary embolism.

At the present time selective pulmonary angiography is widely accepted as the most specific test available for the detection of pulmonary embolism. In addition to detecting pulmonary embolism, hemodynamic studies performed at the time of angiography permit evaluation of the severity of pulmonary vascular obstruction by the emboli. Correlation of angiographic findings with hemodynamic and clinical findings in acute pulmonary embolism has greatly enhanced our understanding of the pathophysiology of this common disorder.

At the Cardiovascular Laboratory of the Peter Bent Brigham Hospital we have utilized selective pulmonary angiography to assess patients suspected of having acute pulmonary embolism since 1964. The results of our experience with 367 angiographic studies of the pulmonary vascula

From the Cardiovascular Laboratory, Peter Bent Brigham Hospital, and Harvard Medical School, Boston, Mass.
Supported in part by grants ([illegible] and [illegible]) from the National Heart Institute, National Institutes of Health, United States Public Health Service.
Received for publication April [illegible] 1970.
Reprint requests to: Dr. James E. Dalen, 721 Huntington Avenue, Boston, Mass. 02115.

Table I

Injection site	*Number of studies*	*Results (%)*		
		Poor	*Satisfactory*	*Excellent*
Right atrium	28	11	86	0
Right ventricle	190	2	5	23
Main pulmonary artery	133	5	75	20

ture during the six year period from 1964 to 1970 will be discussed

Techniques

Selective pulmonary angiography is performed by introducing a No 7F or No 8F closed tip angiographic catheter with multiple side holes via a cutdown of an antecubital vein Under fluoroscopic control the catheter tip is placed in the main pulmonary artery Cardiac output is determined by the Fick or indicator dilution technique Pressures in the pulmonary artery right ventricle right atrium and a systemic artery are measured After collection of these hemodynamic data the catheter is positioned in the main pulmonary artery or in the right ventricular outflow tract Forty to 60 ml of contrast medium is injected with a power injector at a rate of 20 to 30 ml per second A total of 12 chest x rays are taken in the anterior posterior position during held inspiration at time intervals appropriate to visualize the passage of contrast medium through the peak pulmonary arterial phase pulmonary venous phase and the left heart The contrast media used in these studies has been Hypaque-M 75 per cent* or Renografin 76 per cent.† We have noted no significant differences in the technical quality of studies or a difference in patient reaction to these two media.

The earlier techniques of pulmonary angiography utilized injection of contrast medium in a peripheral vein the superior vena cava or the right atrium [1,2,3] In experience injection into the pulmo artery or right ventricle results in a m detailed and more complete visualiza of the pulmonary vasculature. The t nical quality of pulmonary angiograms formed from three different injection is shown in Table I

As noted 14 per cent of the studies formed by injection in the right atr were of poor quality as opposed to 2 per cent and 5 per cent with injectio the right ventricle or main pulmo artery

We have encountered no complicat related to the more central injection Whereas premature ventricular cont tions frequently occur during injection arrhythmias requiring treatment occu in 190 studies in which injection was m in the right ventricle The only two arrh mias related to this procedure in 367 tients occurred when the catheter ent the right atrium (Table III) Furtherm we have observed no evidence that pas of the catheter through the right hear the pulmonary artery has dislodged thro or emboli

The normal pulmonary angiogra

In patients without pulmonary embo or pulmonary vascular disease cont medium injected proximal to or at the monic valve visualizes each lobe of the l at the same time (Fig 1 *A*) Using con tional techniques the main left and r pulmonary arteries, lobar arteries, mental branches and the first two divisions of the segmental arteries visualized

When contrast medium is injected the right ventricular outflow tract or main pulmonary artery at an injection of 20 to 30 ml per second the peak arte phase occurs three to four seconds a injection As shown in Table II the p ence of pulmonary embolism per se d not delay visualization of the peak arte phase

The factors that are associated wit delay in the circulation of contrast medi are clinical evidence of left heart failu low cardiac index and pulmonary hyp tension In the presence of these conditio

*Sodium and meglumine diatrizoates, Winthrop Labs New York, N Y
†Methylglucamine Diatrizoate, E. R. Squibb & Sons, New



Fig. 1. *A* and *B*. Normal pulmonary angiogram. *A*. Arterial phase. Three seconds after injection there is symmetrical filling of the entire pulmonary arterial tree. *B*. Venous phase. Six seconds after injection the contrast medium has filled the pulmonary veins, left atrium, and left ventricle.

Table II. Average time to peak arterial phase (seconds after injection)

Groups	*No. of studies*	*Time (sec.)*
Total group	310	3.7
Angiogram positive for pulmonary embolism	71	3.6
No heart disease	113	3.1
Clinical evidence of congestive heart failure	127	4.2
Cardiac index normal (>3.0 L./min./sq. M.)	129	3.2
Low cardiac index (<2.0 L./min./sq. M.)	50	4.9
Normal pulmonary artery pressure (mean <20 mm. Hg)	116	3.1
Pulmonary hypertension (mean >40 mm. Hg)	60	4.7

timing of films must be adjusted to permit appropriate visualization.

The pulmonary veins from each part of the lungs are visualized simultaneously at an average of three seconds after the peak arterial phase (Fig. 1, *B*).

Indications and contraindications to pulmonary angiography

The only absolute contraindication to this procedure is known allergy to contrast media. In addition, there are two relative contraindications that must be considered: (1) recent myocardial infarction, and (2) ventricular irritability. These two conditions represent relative contraindications because they predispose to the occurrence of ventricular arrhythmias during passage of the catheter to the pulmonary artery. In the presence of these relative contraindications, it is our policy to proceed with pulmonary angiography only if the results of angiography are essential to the determination of the patient's therapy. For example, in the infrequent circumstance where pulmonary embolectomy is a therapeutic consideration, we proceed with angiography in the presence of relative contraindications even in critically ill, hypoxic, and hypotensive patients.

In patients with left bundle branch block, there is the potential that complete heart block will occur when the catheter passes through the right ventricle. Therefore, when performing pulmonary angiography in patients with left bundle branch block, we use a specially designed angiographic catheter that can be used as a unipolar pacemaker.

In the absence of these relative contraindications, it is our policy that the suspicion of pulmonary embolism per se is an indication for pulmonary angiography.

Complications of pulmonary angiography: Morbidity and mortality rates

Complications may occur secondary to cardiac catheterization or as reactions to contrast media. The complications encountered in 367 consecutive patient stud-

Table I

Injection site	Number of studies	Results (%)		
		Poor	Satisfactory	Excellent
Right atrium	28	14	86	0
Right ventricle	190	2	75	23
Main pulmonary artery	133	5	75	20

ture during the six year period from 1964 to 1970 will be discussed

Techniques

Selective pulmonary angiography is performed by introducing a No 7F or No 8F closed tip angiographic catheter with multiple side holes via a cutdown of an antecubital vein Under fluoroscopic control the catheter tip is placed in the main pulmonary artery Cardiac output is determined by the Fick or indicator dilution technique Pressures in the pulmonary artery right ventricle right atrium and a systemic artery are measured After collection of these hemodynamic data the catheter is positioned in the main pulmonary artery or in the right ventricular outflow tract Forty to 60 ml of contrast medium is injected with a power injector at a rate of 20 to 30 ml per second A total of 12 chest x rays are taken in the anterior posterior position during held inspiration at time intervals appropriate to visualize the passage of contrast medium through the peak pulmonary arterial phase pulmonary venous phase and the left heart The contrast media used in these studies has been Hypaque M 75 per cent* or Renografin 76 per cent† We have noted no significant differences in the technical quality of studies or a difference in patient reaction to these two media

The earlier techniques of pulmonary angiography utilized injection of contrast medium in a peripheral vein the superior vena cava or the right atrium.[1,2,3] In our experience injection into the pulmonary artery or right ventricle results in a more detailed and more complete visualization of the pulmonary vasculature The technical quality of pulmonary angiograms performed from three different injection sites is shown in Table I

As noted 14 per cent of the studies performed by injection in the right atrium were of poor quality as opposed to only 2 per cent and 5 per cent with injection in the right ventricle or main pulmonary artery

We have encountered no complications related to the more central injection sites Whereas premature ventricular contractions frequently occur during injection, no arrhythmias requiring treatment occurred in 190 studies in which injection was made in the right ventricle. The only two arrhythmias related to this procedure in 367 patients occurred when the catheter entered the right atrium (Table III) Furthermore we have observed no evidence that passage of the catheter through the right heart to the pulmonary artery has dislodged thrombi or emboli

The normal pulmonary angiogram

In patients without pulmonary embolism or pulmonary vascular disease contrast medium injected proximal to or at the pulmonic valve visualizes each lobe of the lung at the same time (Fig 1 4) Using conventional techniques the main left and right pulmonary arteries, lobar arteries segmental branches and the first two subdivisions of the segmental arteries are visualized

When contrast medium is injected into the right ventricular outflow tract or the main pulmonary artery at an injection rate of 20 to 30 ml per second the peak arterial phase occurs three to four seconds after injection As shown in Table II the presence of pulmonary embolism per se does not delay visualization of the peak arterial phase

The factors that are associated with a delay in the circulation of contrast medium are clinical evidence of left heart failure low cardiac index and pulmonary hypertension In the presence of these conditions

*Sodium and meglumine diatrizoates, Winthrop Labs New York, N Y
†Methylglucamine Diatrizoat E. R. Squibb & Sons, New

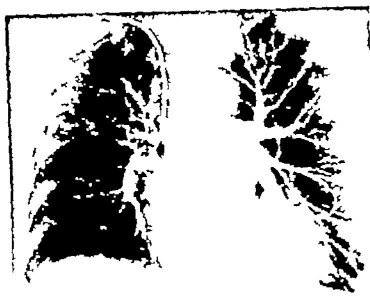


Fig 2 I traluminal filling defects Filling defects are ell visualized in the right upper lobe and in the ight lower lobe A large nonobstructing filling defect in the left pulmonary artery (arrow) is d'fficult to visualize in this view because contrast medium surround it. Note that none of the filling defect have caused complete obstruction therefore there is minimal oligemia

clot was rendered radiopaque by the addi tion of Dionosil so that the emboli could be localized by plain chest x rays taken after embolization Selective pulmonary angiograms n three projections were taken at intervals after embolization and were compared with the baseline angiograms.

These experimental studies demonstrated that the presence of thromboemboli in the pulmonary circulation can cause four dif ferent angiographic abnormalities

1 *Intraluminal filling defects* (Fig 2) This most specific sign of pulmonary embolism was not detected in all cases. A large incompletely obstructing embolus may not be detected because it is obscured by contrast medium flow ing around t.

2 *Cutoffs of rteries* (Fig 3) As with intralum nal filling defects, this finding was not seen w th all emboli Cutoffs occur only if an embolus causes com plete occlusion of an artery More frequently the embolus straddles a bifurcation and causes partial occlusion of each branch If an artery is occluded near its origin a cutoff may be recognized only if the absence of that specific artery is detected

3 *Areas of ol gemia* (Fig 4) Areas of the lung that are distal to a completely obstructed artery are not perfused and thus will appear oligemic by angiography However oligemia may also occur in portions of the vascula ture that are distal to incomplete embolic occlusion In this circumstance if the embolus itself is not recognized as an intraluminal filling defect, embolism will be evidenced only by the area of oligemia distal to the site of unrecognized incomplete embolic obstruction. Oligemia may also result from embolic occlusion of multiple small peripheral arterial branches in a given area of the lung In this circumstance the embolized area may appear pruned " i.e. the arterial tree in that area may appear as a tree pruned of its small branches.

4 *Asymmetry of flow* When contrast medium is injected at or proximal to the pulmonic valve, it flows at the

Glaxo Laboratories Ltd., Greenford, En-

Table III. Complications of pulmonary angiography in 367 consecutive patients

Variables	Number	Fatal
I. Related to cardiac catheterization		
Cardiac perforation	2	0
Pyrogen reaction	3	0
Arrhythmia	2	0
II. Related to angiography		
Bronchospasm	3	0
Angioneurotic edema	1	0
Anaphylaxis	1	0
Cardiogenic shock	1	1
Total	13 (4%)	1 (0.3%)

ies over a six year period in our laboratory are shown in Table III.

There were seven complications related to cardiac catheterization and six related to angiography per se. The total incidence of complications was 4 per cent.

Two cardiac perforations occurred in the first 50 patients to be studied by pulmonary angiography in this laboratory. Both perforations occurred during passage of the catheter to the pulmonary artery and were judged to be related to the use of a stiff nylon core angiographic catheter. With the use of a more pliable woven dacron angiographic catheter* there have been no perforations in more than 300 consecutive angiographic studies. Pyrogen reactions occurred in three patients and were treated with acetylsalicylic acid. Two patients developed rapid atrial fibrillation when the catheter entered the right atrium. In each case the arrhythmia was controlled with digitalis and normal sinus rhythm was restored within 24 hours.

The most common complication related to contrast media was acute bronchospasm. Each of the three episodes of bronchospasm occurred in patients with a history of bronchial asthma and each episode was relieved by intravenous epinephrine (1 to 5 ml. of 1:100,000 solution).

The only death related to the procedure occurred in a 36-year-old woman with terminal primary pulmonary hypertension and recent acute pulmonary embolism. Cardiogenic shock with electromechanical dissociation occurred immediately after injection of 40 ml. of contrast media. Cardiac resuscitation was unsuccessful.

One additional death occurred during this six year period. In this patient emergency pulmonary angiography was performed thirty minutes after she had been resuscitated from cardiac arrest which was judged to have been due to massive pulmonary embolism. Throughout the angiographic procedure she was ventilated through an endotracheal tube and marked hypotension persisted despite vasopressors. Pulmonary angiography demonstrated massive central pulmonary embolism. Twenty minutes after the angiogram had been performed, while preparations were being made for pulmonary embolectomy with cardiopulmonary bypass, hypotension became more severe and cardiac arrest recurred. Emergency Trendelenburg embolectomy was performed in the cardiac catheterization laboratory. Although large central pulmonary emboli were removed, the patient could not be resuscitated. Her death was attributed to massive pulmonary embolism; it did not appear to have been precipitated by pulmonary angiography. Seven other patients with massive pulmonary embolism have subsequently undergone emergency pulmonary angiography without untoward reactions despite the presence of hypotension requiring vasopressors throughout the procedure.

Angiographic findings in pulmonary embolism

The most diagnostic finding in pulmonary embolism is visualization of an intra-arterial embolus as a negative intraluminal filling defect outlined by surrounding radiopaque contrast medium. However, pulmonary embolism may be present without this specific finding and embolism may cause certain other angiographic abnormalities. These abnormalities have been documented in this laboratory[11,12] using intact anesthetized dogs. After baseline pulmonary angiograms were taken, dogs were embolized with 3 to 10 ml. of autologous blood clot. In some cases the blood

*Eppendorf United States Catheter and Instrument Corp., Glens Falls, N. Y.

same rate to each part of the lungs. When incomplete embolic occlusion occurs, it may cause a delay in filling of the arterial tree distal to the point of incomplete occlusion. There may be associated oligemia of this area of the lung or perfusion of this area may be complete even though delayed.

We have shown that each of these four angiographic abnormalities (intraluminal filling defects, cutoffs, oligemia, and asymmetry of flow) occur when healthy dogs are embolized with autologous blood clot. These same four angiographic abnormalities also occur in patients with pulmonary embolism.

In patients in whom the diagnosis of pulmonary embolism is certain because of the visualization of intraluminal filling defects and/or cutoffs, areas of oligemia and asymmetry of flow are frequently present. However, in patients who have chronic lung disease or congestive heart failure, these latter two abnormalities, oligemia and asymmetry of flow, may occur in the absence of pulmonary embolism.

The angiographic abnormalities associated with embolism in patients with and without coexistent chronic lung disease or congestive heart failure were assessed in this laboratory by Stein and associates.[11] They found that filling defects and cutoffs occur only in patients with pulmonary embolism. These two abnormalities were not present in patients with chronic lung disease or congestive heart failure without pulmonary embolism. However, oligemia and asymmetry of blood flow, although very frequent in documented pulmonary embolism, also occurred in association with chronic lung disease or congestive heart failure in the absence of pulmonary embolism.

Oligemia may occur in association with emphysematous blebs in patients with chronic lung disease and may mimic pulmonary embolism as shown in Fig. 5.

Asymmetry of flow is often seen in patients with heart disease that has caused increased pulmonary venous pressure (e.g., secondary to left ventricular failure or mitral stenosis). With significant elevation of pulmonary venous pressure, peak flow to both lower lobes may occur one to three seconds after peak visualization of the upper lobar arteries (Fig. 6). The relation



Fig. 5. Oligemia without pulmonary embolism. In this patient with chronic lung disease, there was no clinical or angiographic evidence of pulmonary embolism. Extensive areas of oligemia are present in the right lung and the left upper lobe. These areas of oligemia correspond to emphysematous blebs evident on plain chest roentgenogram.

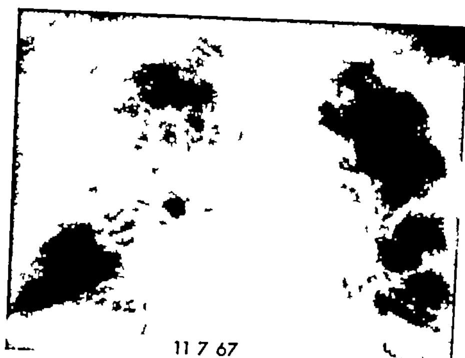


Fig 3 Cutoff of arteries. A large intraluminal filling defect is present in the left pulmonary artery distal the origin of the left upper lobar artery Although the filling defect is indistinct, the artery is cut off at th point with resultant distal oligemia



Fig 4 Oligemia due to pulmonary embolism Multiple filling defects in the right pulmonary artery have obstructed blood flow with resultant oligemia of the entire right lung In the left lower lobe, an area of oligemia has occurred secondary to an obstructed segmental artery Note the hyperemia of the only normal portion of the vasculature, the left upper lobe.

Chart I

Diagnosis	No. of patients	%
Definite pulmonary embolism	89	36
Probable pulmonary embolism	22	9
Equivocal	42	17
Negative	94	38

Chart II

Diagnosis	No.	%
Intraluminal filling defects	71	80
Cutoff	55	62
Oligemia	67	75
Asymmetry of flow	62	70

graphic diagnosis of definite pulmonary embolism all 89 patients had intraluminal filling defects and/or cutoffs. The high incidence of the less diagnostic findings, oligemia (75 per cent) and asymmetry of flow (70 per cent) is evident.

In these 89 patients, evidence of embolism was rarely limited to one artery or one lobe In 47 per cent of these cases, filling defects were present in both lungs. This is consistent with observations made at post mortem by Smith Dexter and Dammin Utilizing postmortem arteriography in 34 patients with pulmonary embolism they found that in each case multiple emboli were widely scattered through all segments of the lungs.

Probable pulmonary embolism Each of the 22 patients whose angiogram was interpreted as probable pulmonary embolism had asymmetry of flow (86 per cent) and/or oligemia (50 per cent) in the absence of lung disease or congestive heart failure. In addition 50 per cent had possible intraluminal filling defects and 41 per cent had possible cutoffs. Each of these patients was treated for acute pulmonary embolism

Equivocal The 42 patients in whom pulmonary embolism was neither excluded nor established by the angiographic study highlight the shortcoming of this technique. In these patients, the decision regarding therapy was of necessity based on the clinical findings.

In 10 patients the diagnosis was equivocal due to the fact that the angiographic study was of suboptimal technical quality Suboptimal studies were most common in patients with congestive failure, chronic lung disease or obesity As noted technically poor studies were especially common when injection was made in the right atrium rather than the right ventricle or pulmonary artery (Table I)

In the remaining 32 patients, the study was equivocal because of the presence of nondiagnostic abnormalities i.e possible filling defects or cutoffs, or oligemia and/or asymmetrical flow in patients with preexistent heart disease or lung disease.

Heart disease with congestive failure presents a particular problem in the interpretation of pulmonary angiograms. Of 117 patients without previous heart disease the angiographic study was equivocal for pulmonary embolism in only 11 per cent whereas in 125 patients with coexistent congestive heart failure equivocal studies were obtained in 21 per cent. There was no increase in the per cent of equivocal studies in 60 patients studied more than four weeks after the onset of symptoms (19 per cent) than in the 147 patients studied within four weeks of the onset of symptoms (17 per cent)

Negative angiographic studies Ninety four (38 per cent) of the 247 patients clinically suspected of acute pulmonary embolism had no evidence of pulmonary embolism at angiography We believe that this high percentage of negative studies can be attributed to two factors.

It has been our philosophy that in patients without relative contraindications, the risks of pulmonary angiography are less than the risks of inappropriate surgical or medical therapy of presumed pulmonary embolism Therefore the primary indication for angiography in this group of patients was suspicion of pulmonary embolism. Rigorous criteria for the clinical diagnosis were not employed in selecting patients for angiography Thus, the high percentage of negative studies in this series may be a reflection of the difficulties of the clinical diagnosis of pulmonary embolism



Fig. 6. *A* and *B*. Asymmetry of flow without pulmonary embolism. *A*, Two seconds after injection the contrast extends to the periphery of the upper lobes, but has not filled the lower lobes. *B*, Four seconds after injection contrast has filled the lower lobes indicating that the vasculature in the lower lobes is intact. This patient had mitral stenosis with a left atrial mean pressure of 20 mm. Hg. There was no clinical or angiographic evidence of pulmonary embolism.

Table IV. Relationship between pulmonary capillary wedge pressure and flow pattern to lower lobes in patients without pulmonary embolism

Pulmonary capillary wedge pressure (mean mm. Hg)	*No. of studies*	*Patients with bilateral lower lobe delay (%)*
<12	105	11
13-20	15	20
>20	27	48

ship of this flow abnormality, bilateral lower lobe delay, to pulmonary venous pressure (as reflected by pulmonary capillary pressure) in patients without pulmonary embolism is shown in Table IV.

Whereas delay of flow to the lower lobes was uncommon when pulmonary capillary wedge pressure was less than 20 mm. Hg, bilateral lower lobe delay occurred in 48 per cent of 27 patients with a pulmonary capillary wedge pressure of more than 20 mm. Hg.

On the basis of these experimental and clinical observations we utilize the following criteria in the diagnosis of pulmonary embolism by pulmonary angiography:

1. *Definite pulmonary embolism*. Intraluminal filling defects and/or cutoffs of arteries.
2. *Probable pulmonary embolism*. Oligemia and/or asymmetry of blood flow in patients who do not have coexistent lung disease or heart disease.
3. *Equivocal*. Presence of oligemia and/or asymmetry of blood flow in patients with lung disease or heart disease or presence of uncertain abnormalities, i.e., possible filling defect or possible cutoff.
4. *Negative*. No angiographic abnormalities consistent with pulmonary embolism.

Angiographic findings in patients suspected of acute pulmonary embolism

The angiographic diagnosis (using the above criteria) in 247 consecutive patients suspected of acute pulmonary embolism (symptoms within four weeks of the study) are shown in Chart I.

As can be seen, a definitive angiographic diagnosis, i.e., definite pulmonary embolism or negative for pulmonary embolism (normal angiogram) was made in 74 per cent of the 247 patients. The current limitation of this technique is reflected by the large number of studies (17 per cent) which were interpreted as equivocal. In these latter cases pulmonary embolism was neither established nor excluded by the angiographic study.

Definite pulmonary embolism. The angiographic abnormalities present in the 89 patients with angiographic abnormalities interpreted as demonstrating definite pulmonary embolism are shown in Chart II.

As a result of our criteria for an angio-

Chart I

Diagnosis	No. of patients	%
Definite pulmonary embolism	89	36
Probable pulmonary embolism	22	9
Equivocal	42	17
Negative	94	38

Chart II

Criterion	No.	%
Intraluminal filling defects	71	80
Cutoff	55	62
Oligemia	67	75
Asymmetry of flow	62	70

graphic diagnosis of definite pulmonary embolism all 89 patients had intraluminal filling defects and/or cutoffs. The high incidence of the less diagnostic findings, oligemia (75 per cent) and asymmetry of flow (70 per cent) is evident

In these 89 patients, evidence of embolism was rarely limited to one artery or one lobe. In 47 per cent of these cases, filling defects were present in both lungs. This is consistent with observations made at post mortem by Smith Dexter and Dammin[14] Utilizing postmortem arteriography in 54 patients with pulmonary embolism they found that in each case multiple emboli were widely scattered through all segments of the lungs.

Probable pulmonary embolism Each of the 22 patients whose angiogram was interpreted as probable pulmonary embolism had asymmetry of flow (86 per cent) and/or oligemia (50 per cent) in the absence of lung disease or congestive heart failure In addition 50 per cent had possible intraluminal filling defects and 41 per cent had possible cutoffs. Each of these patients was treated for acute pulmonary embolism

Equivocal The 42 patients in whom pulmonary embolism was neither excluded nor established by the angiographic study highlight the shortcoming of this technique. In these patients the decision regarding therapy was of necessity based on the clinical findings.

In 10 patients the diagnosis was equivocal due to the fact that the angiographic study was of suboptimal technical quality Suboptimal studies were most common in patients with congestive failure, chronic lung disease, or obesity As noted technically poor studies were especially common when injection was made in the right atrium rather than the right ventricle or pulmonary artery (Table I)

In the remaining 32 patients the study was equivocal because of the presence of nondiagnostic abnormalities i.e. possible filling defects or cutoffs, or oligemia and/or asymmetrical flow in patients with preexistent heart disease or lung disease.

Heart disease with congestive failure presents a particular problem in the interpretation of pulmonary angiograms. Of 117 patients without previous heart disease the angiographic study was equivocal for pulmonary embolism in only 11 per cent whereas, in 125 patients with coexistent congestive heart failure equivocal studies were obtained in 21 per cent. There was no increase in the per cent of equivocal studies in 60 patients studied more than four weeks after the onset of symptoms (19 per cent) than in the 247 patients studied within four weeks of the onset of symptoms (17 per cent)

Negative angiographic studies Ninety four (38 per cent) of the 247 patients clinically suspected of acute pulmonary embolism had no evidence of pulmonary embolism at angiography We believe that this high percentage of negative studies can be attributed to two factors.

It has been our philosophy that in patients without relative contraindications, the risks of pulmonary angiography are less than the risks of inappropriate surgical or medical therapy of presumed pulmonary embolism Therefore the primary indication for angiography in this group of patients was suspicion of pulmonary embolism Rigorous criteria for the clinical diagnosis were not employed in selecting patients for angiography Thus, the high percentage of negative studies in this series may be a reflection of the difficulties of the clinical diagnosis of pulmonary embolism

Table V Comparison of premortem angiography with postmortem findings

Premortem angiographic diagnosis	Postmortem diagnosis	
	Pulmonary embolism	No pulmonary embolism
Definite pulmonary embolism	7	0
Probable pulmonary embolism	1	0
Equivocal	1	2
Negative	0	6

The second factor to be considered is that a negative angiographic study may not per se exclude embolism that is limited to arteries that are too small to be visualized by conventional angiography It is difficult to determine how often embolism may be limited to third order or lobular arteries and still present symptoms. At postmortem embolic obstruction of these small arteries is very common [16]

Of the 94 patients with normal pulmonary angiograms 53 had lung scans Forty three of these 53 lung scans were abnormal However 21 of these 43 patients had an infiltrate and/or pleural effusion by chest x ray at the time of lung scan Thus the perfusion defects noted by lung scan may have been due to abnormalities other than pulmonary embolism [13,14] It is also possible that some of these patients with an abnormal lung scan but normal pulmonary angiogram had embolism limited to the smallest branches of the pulmonary vasculature

Validity of the angiographic diagnosis of pulmonary embolism

The ultimate criterion for the accuracy of interpretation of pulmonary angiograms is postmortem examination of the lungs However comparison of angiographic and postmortem findings is pertinent only if the postmortem examination is performed in close proximity to the premortem angiographic study Significant resolution of pulmonary embolism may occur in periods longer than two weeks [17]

During this five year period 17 of our patients who had been studied by pulmonary angiography died and had post mortem examination within two weeks of the angiographic study

Of seven patients with an angiographic diagnosis of definite pulmonary embolism and one with probable pulmonary embolism all eight had embolism at postmortem. Thus there were no false positive angiographic diagnoses. Of six patients with a negative pulmonary angiogram studied at postmortem none had pulmonary emboli. However of the three patients with a diagnosis of equivocal one had emboli at postmortem examination and two did not.

It is our conclusion that using the angiographic criteria that we have outlined false positive angiographic diagnoses of pulmonary embolism are rare. False negative diagnoses present a potential problem Since pulmonary embolism may be present without demonstrable filling defects or cut offs, reliance upon these two criteria for a definitive diagnosis allows the potential of a false negative diagnosis. However since embolism rarely occurs without at least a nonspecific angiographic abnormality most false negative interpretations would be categorized in the equivocal or probable group by our criteria It is our policy to treat for pulmonary embolism when the angiogram is definite or probable and to treat most patients whose angiograms are read as equivocal

We believe that it is sufficiently important to avoid false positive angiographic diagnosis, that we tolerate a sizeable percentage of equivocal interpretations We anticipate that the use of magnification angiographic techniques[18] and the use of selective cineangiography[19] as an adjunct to conventional pulmonary angiography will permit the more accurate recognition of embolism in studies currently interpreted as equivocal

Summary

Pulmonary angiography is the most specific test available for the diagnosis of acute pulmonary embolism This technique can safely be performed in critically ill patients. In 367 consecutive studies our incidence of complications has been 4 per cent and there has been only one death

Hemodynamic studies done as part of

the procedure permit evaluation of the severity and the pathophysiology of acute pulmonary embolism

The two diagnostic angiographic findings of pulmonary embolism are intraluminal filling defects and cutoff arteries. Oligemia and asymmetry of blood flow are frequently seen in pulmonary embolism but are not specific. These latter two abnormalities may occur in chronic lung disease or congestive heart failure without pulmonary embolism.

Using these diagnostic criteria in 247 patients studied because of a clinical diagnosis of acute pulmonary embolism a definitive diagnosis (either definite pulmonary embolism or negative) was established by angiography in 74 per cent. In 9 per cent the diagnosis was probable pulmonary embolism and in 17 per cent the findings were equivocal for pulmonary embolism.

Application of these diagnostic criteria results in minimal false positive angiographic diagnoses. False negative diagnoses may occur if embolism is limited to peripheral branches of the pulmonary vasculature that are not visualized by current angiographic techniques. The incidence of symptomatic pulmonary embolism limited to these small arteries is uncertain.

The primary limitation of this technique is, that in patients with underlying heart disease or chronic lung disease the results of angiography may be equivocal The application of new techniques of magnification angiography and/or selective cine angiography offer promise in enhancing the recognition of embolism in this group of patients.

REFERENCES

1. Carvalho, L. and Moniz, E. Visibility of the pulmonary vessels (angiopneumography). Acta Radiol. Lisbon 14:433, 1933.
2. Robb, G. P. and Steinberg, I. Visualization of the chambers of the heart, the pulmonary circulation, and the great blood vessels in man, Amer. J. Roentgen. 41:1, 1939.
3. Carroll, D. Chronic obstruction of major pulmonary arteries, Amer. J. Med. 9:175, 1950.
4. Davison, P. H. Armitage, G. H., and M. Ilvaen, D. J. S. Chronic cor pulmonale due to silent pulmonary embolism, Lancet 2:224, 1956.
5. Ehrner, L. Garfied, T. and Linderholm, H. Chronic cor pulmonale following thromboembolism, Acta Med. Scand. 161:279, 1959.
6. Chrispin, A. R., Goodwin, J. F. and Steiner, R. E. The radiology of obliterative pulmonary hypertension and thromboembolism, Brit. J. Radiol. 36:705, 1963.
7. Williams, J. R., and Wilcox, W. C. Pulmonary embolism: roentgenographic and angiographic considerations, Amer. J. Roentgen. Rad. Therapy and Nuclear Med. 89:333, 1963.
8. Sasahara, A. A. Stein, M. Simon, M. and Littmann, D. Pulmonary angiography in the diagnosis of thromboembolic disease. New Eng. J. Med. 270:1075, 1964.
9. Alexander, J. K., Lewis, J. M. Axelrad, M. A., Lockhart, R. W. and Fred, H. L.: Cardiorespiratory function in patients with acute pulmonary thromboembolism demonstrated angiographically. Clin. Res. 13:346, 1965.
10. Stein, P. D. Mathur, V. S., Herman, M. V., and Levine, H. D. Complete heart block induced during cardiac catheterization of patient with preexistent bundle branch block, Circulation 31:783, 1966.
11. Dalen, J. E., Mathur, V. S., Evans, H., Haynes, F. W. Pur Shahriari, A. A., Stein, P. D. and Dexter, L. Pulmonary angiography in experimental pulmonary embolism, Amer. Heart J. 72:509, 1966.
12. Mathur, V. S., Dalen, J. E., Evans, H., Haynes, F. W. Pur Shahriari, A. A., Stein, P. D. and Dexter, L. Pulmonary angiography one to seven days after experimental pulmonary embolism, Invest. Radiol. 2:304, 1967.
13. Stein, P. D. O'Connor, J. F., Dalen, J. E., Pur Shahriari, A. A., Hoppin, F. G., J. Hammond, D. T. Haynes, F. W. Fleischner, F. G., and Dexter, L.: The angiographic diagnosis of acute pulmonary embolism: evaluation of criteria, Amer. Heart J. 73:730, 1967.
14. Smith, G. T. Dexter, L., and Dammin, G. J.: Postmortem quantitative studies in pulmonary embolism, in Sasahara, A. A., and Stein, M. editors. Pulmonary embolic disease. New York, 1965, Grune & Stratton, Inc., p. 120.
15. Poulose, K., Reba, R. C., and Wagner, H. N. J. Characterization of the shape and location of perfusion defects in certain pulmonary diseases, New Eng. J. Med. 279:1020, 1968.
16. Quinn, J. L., III. The lung: the challenge of nuclear medicine, Amer. J. Roentgen. 103:251, 1969.
17. Dalen, J. E., Banas, J. S., J. Brooks, H. L., Evans, G. L., Paraskos, J. A. and Dexter, L.: Resolution rate of acute pulmonary embolism in man, New Eng. J. Med. 280:1194, 1969.
18. Greenspan, R. H., Simon, A. L., Ricketts, H. J. Rojas, R. H., and Watson, J. C.: In vivo magnification angiography. Invest. Radiol. 2:419, 1967.
19. Brooks, H., Meister, S., Szucs, M. J. Banas, J. J. Dexter, L., and Dalen, J. Selective cineangiography in the diagnosis of pulmonary embolism, Circulation 40:III-51, 1969 (Suppl. III).

The effect of prolonged bed rest on postpartal cardiomyopathy

G. E. Burch, M.D.
C. D. McDonald, M.D.
J. J. Walsh, M.D.
New Orleans, La.

Nonvalvular myocardial disease of unknown etiology associated with the postpartal period was first described over a century ago.[1] Although reported from many parts of the world, including North and South America, Europe, Asia, and Africa, the cardiomyopathy occurs most frequently among Negroes in warm climates.[2] Postpartal heart disease has been a well recognized clinical entity at the Charity Hospital in New Orleans for several decades.[3-8] However, geographic differences in incidence as well as the lack of a demonstrated etiology or specific pathologic picture have discouraged general acceptance of the syndrome.[9,10]

This report relates some of our experiences with 34 patients with postpartal heart disease who were admitted to the Bed Rest Program at the United States Public Health Service Hospital in New Orleans. Earlier data on the first 15 patients comprised a previous report.[11]

Clinical material and methods

Patients were referred to the Bed Rest Study from the Tulane Medical Service of the Charity Hospital. Criteria for admission to the study consisted of (1) absence of history, symptoms, and physical findings of heart disease prior to the puerperium, (2) appearance of signs and symptoms of cardiomyopathy between the second and twentieth week of the puerperium, and (3) inability to establish an etiologic basis for the heart disease. These criteria were applied to eliminate patients who developed mild heart failure during delivery as well as those with possible pre-existing cardiac disease that became clinically apparent during or shortly following pregnancy.

Patients meeting these criteria were transferred to our special cardiovascular research unit at the United States Public Health Service Hospital in New Orleans for the program of prolonged bed rest in

From the Department of Medicine of the Tulane University School of Medicine, the United States Public Health Service Hospital, the Charity Hospital of Louisiana, and the Veterans Administration Hospital, New Orleans, La.

Supported by Grant HE-06769 from the National Heart Institute of the United States Public Health Service and grants from the Rudolph Matas Memorial Fund for the Kate Prewitt Hess Laboratory and the Rowell A. Billups Fund for Research in Heart Disease.

Received for publication April 17, 1970.

Reprint requests to: G. E. Burch, M.D., Department of Medicine, Tulane University School of Medicine, 1430 Tulane Ave., New Orleans, La. 70112.

the treatment of the "big" heart. The operation of this clinical research unit has been previously described.[8] Because of the stress of a hot and humid climate on myocardial function the unit is air-conditioned.[8,4] The initial period of bed rest for these 34 patients varied from 5 to 597 days (mean 207 days) depending upon the clinical response and cooperation of the patient. Ambulation was usually not begun until three months after heart size had returned to normal and the patients were clinically well. In those patients in whom a normal heart size was not achieved ambulation was begun when no further reduction in heart size had occurred over a 6 to 12 month period of bed rest. In addition to prolonged bed rest, all patients received conventional medical therapy for congestive heart failure including sodium restriction digitalis, diuretics, and when indicated anticoagulants. All patients underwent extensive evaluation in search of an etiology for their heart disease.

Upon discharge, patients were followed in a cardiomyopathy clinic. Many were readmitted for further periods of bed rest because of recurrence of congestive heart failure or cardiomegaly. Follow-up varied from 10 days to 12 years (mean follow up 5 years).

With subsequent pregnancies patients have been admitted to the hospital for bed rest 2 to 4 months prior to delivery. When advisable patients have undergone sterilization procedures. In the remaining patients intrauterine devices have been advised. Hormonal suppression of ovulation has been avoided.

Clinical history

Age at onset of heart disease and race of the patients are summarized in Table I. Thirty two patients were Negro in keeping with earlier reports. [4] All patients were housewives however some had been employed previously for various periods of time as domestic servants.

Nineteen patients were aware of hypertensive or atherosclerotic heart disease in one or both parents. Two patients reported heart disease of obscure type in siblings less than 35 years of age. With careful questioning 11 patients recalled symptoms compatible with an upper respiratory infection during the 6 weeks preceding the onset of their illness. Appropriate viral studies were not done. Although post infectious myocarditis has been invoked in the pathogenesis of cardiomyopathy[15] convincing evidence was lacking in these 11 patients since the symptoms were vague and possibly related to early left ventricular failure.

Careful dietary histories in the 34 patients revealed adequate nutrition in only 7. The other 27 patients usually ate less than three meals per day and consumed diets high in fat and starch low in protein and virtually devoid of fresh fruits and vegetables. These dietary patterns were established during childhood and not altered during frequent pregnancies, hard work, and prolonged periods of lactation. As a rule the socioeconomic backgrounds revealed families of 6 or more persons living in two- and three-room quarters with monthly incomes of less than 200 dollars.

Consumption of alcohol was not striking. Four patients had sporadically consumed whiskey in amounts greater than one fifth per week for periods in excess of a year. Eleven patients occasionally drank "socially" but not more than a half pint per week. The remaining 19 patients denied alcohol consumption completely.

Obstetrical histories revealed a striking association of cardiomyopathy with multiparity (Table II). In only 4 patients did the onset of heart disease follow the first pregnancy. The 34 patients had had a total of 155 pregnancies before the onset of their heart disease including 16 abortions among 11 of the patients and 9 stillbirths among 5 of the patients. There were 11 cesarean sections performed for various obstetrical complications. One patient had documented toxemia of pregnancy with papilledema and eclamptic seizures with a previous pregnancy. Twenty two patients gave histories of "pre-eclampsia" with previous pregnancies, the precise definition and implication of which could often not be determined on careful review of the obstetrical records.

Exertional dyspnea, orthopnea, and cough were usually the initial symptoms and reflected the occurrence of left ven

Table I. Age at onset of heart disease and race of 34 patients with postpartal cardiomyopathy

Race	Age at onset of heart disease (yr.)					
	19 or less	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44
Caucasian	—	1	—	1	—	—
Negro	4	7	6	6	6	3
Total	4	8	6	7	6	3

Table II. Number of pregnancies at onset of heart disease

Pregnancy number at onset of heart disease	1	2	3	4	5	6	7	8	9	10
Number of patients	4	5	6	5	4	1	—	2	5	2

Table III. Postpartal cardiomyopathy (34 patients)

Symptoms on admission	No. of patients	Physical findings on admission	No. of patients
Dyspnea on exertion	34	Cardiomegaly	34
Orthopnea	30	Apical pansystolic murmur	20
Edema	26	Protodiastolic gallop rhythm	19
Cough	25	Edema	17
Paroxysmal nocturnal dyspnea	23	Hepatomegaly	17
Weakness	17	Accentuated P_2	14
Palpitations	13	Moist râles	11
Ascites	8	Cervical venous distention	9
Chest pains	8	Cardiac arrhythmia	9
Hemoptysis	7		
Abdominal pains	6		

tricular congestive heart failure (Table III). This was usually followed shortly by right ventricular congestive heart failure as manifested by systemic venous hypertension, edema, ascites, and abdominal pains. Chest pains or hemoptysis occurred in 14 patients, 8 of whom subsequently had clinical or autopsy evidence of pulmonary embolization. Three patients had emboli to cerebral vessels and 1 patient had an embolus to the superficial femoral artery.

All patients exhibited clinical cardiomegaly. In 20 patients there was an apical pansystolic murmur of mitral regurgitation probably due to ventricular dilatation and associated papillary muscle dysfunction (Table III). A diastolic gallop rhythm was present in 19 patients. Approximately one half of the patients were found to have an accentuation of the pulmonic component of the second heart sound; hepatomegaly and edema. Crepitant râles, cervical venous distention, and cardiac arrhythmia were encountered in approximately one third of the patients. Exertional dyspnea, orthropnea, and cough occurring in 34, 30, and 25 patients, respectively, were usually among the initial symptoms and reflected the occurrence of left ventricular congestive heart failure.

Initial radiographic studies of the chest



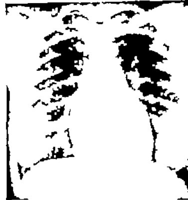
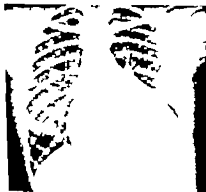


Fig. 1 Teleroentgenograms of 28-year-old Negro oman ith postpartal cardiomyopathy showing, *A* cardiomegaly on admission nd, *B* return of heart size t normal 18 months later follow ng 12 months of bed rest and 6 months as an outpatient.



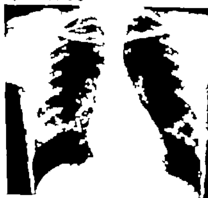


Fig. 2 Chest x-rays of 35-year-old Negro oman with postpartal cardiomyopathy showing, *A* cardiomegaly on initial admission to the prolonged bed rest program and, *B* normal heart size as long as 6 years later

including fluoroscopy with barium in the esophagus, revealed generalized cardiomegaly in all patients (Figs. 1 to 4) Not in frequently enlargement of the left atrium was also noted

All patients had abnormal electrocardiograms (Fig 5) The most frequent abnormalities were inverted biphasic, or flattened T waves usually in the precordial leads and most commonly in V through V 6. T wave abnormalities were also observed in the right precordial and standard leads and were usually accompanied by depression of the S-T segments. Twenty three patients had prominent R waves in V and V with deep S waves in the right precordial leads. Twenty-six patients showed poor R wave progression so that a dominant R wave did not appear until V 4. The mean QRS axis was normal in 24 patients, to the left in 9 and to the right in one. The QRS interval was greater than 0 10 second in 5 patients 2 of whom had left bundle branch block. Slurred notched and deformed R waves of diffuse myocardial disease and defective intraventricular con



Fig 3 Teleoroentgenograms of a 31 year-old Negro woman with postpartal cardiomyopathy and pulmonary embolism showing *A* cardiomegaly on admission and *B* failure of the heart to respond to therapy after 13 months of bed rest

duction were common Sixteen patients had absence of septal Q waves in Leads I V_5, and V_6 indicating septal fibrosis and/or degeneration

The P R interval was prolonged in 9 patients There were biphasic P waves in V_1 and V_2 with notching in the standard leads in 22 patients Peaking of the P wave in Lead II occurred in 5 patients All patients were in sinus rhythm and sinus tachycardia was present prior to therapy Premature ventricular contractions were frequently observed

The spatial vectorcardiograms, recorded by means of the equilateral tetrahedral reference system in 25 patients, revealed further the electric alterations (Fig 5) The QRS sÊ loop was posteriorly oriented in 18 patients, and there was more superior orientation than usual in 14 patients. Another characteristic observed was marked deformities of the QRS sÊ loop This was most evident in the left sagittal plane projection The rotation of the QRS-sÊ loop was counterclockwise in the frontal plane projection in 15 patients

In addition to cardiovascular studies all patients underwent a general medical evaluation A hypochromic microcytic anemia was noted with hemoglobin values of less than 12 Gm per cent in 18 patients The response to diet and supplemental iron was favorable All patients had normal total and differential white blood cell counts

Hemoglobin electrophoresis perfomed in 24 of the Negro patients revealed type A hemoglobin in 13 patients, AS in 6 and AC in 5 Blood groupings were determined in 26 patients. There were 17 patients with type O 4 with type B and 5 with type A blood All 26 patients were Rh positive

Three patients had positive serologic tests for syphilis A history of adequate treatment for syphilis could be established in each instance All patients had multiple negative lupus erythematosus preparations. Antistreptolysin-O titers were elevated in 2 patients but subsequently returned to normal levels Four patients had a one-plus C reactive protein for which no cause could be determined Elevated toxoplasin hemagglutination inhibition titers were present in 4 patients.

Abnormalities of urinalysis consisted of either proteinuria pyuria or cylindruria in 30 patients. Eighteen patients exhibited impaired ability of renal concentration with water deprivation In 4 patients azotemia occurred terminally

Total serum cholesterol levels above 250 mg per cent were noted in 10 patients. One of these patients had a diabetic glucose tolerance curve Three patients had a serum

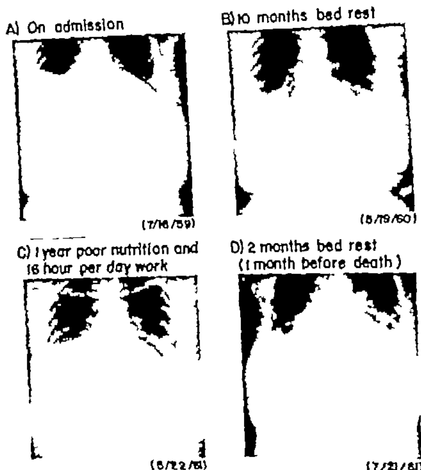


Fig. 4. Serial teleoroentgenograms of 36-year-old Negro woman with postpartal cardiomyopathy. *A*. The x-ray on admission showed cardiomegaly. *B*. Following 10 months of bed rest the heart returned almost to normal size. *C*. One year later after patient returned to an inadequate diet and a 16 hour per day work schedule following discharge from hospital the heart again was enlarged. *D*. The heart failed to respond to therapy after readmission and 2 months of bed rest (1 month prior to death).

albumin below 3.5 Gm. per cent. In 2 of these patients the total serum proteins were less than 6.0 Gm. per cent. One of the patients with a positive test from the Venereal Disease Research Laboratory had a reversed albumin-globulin ratio with a serum globulin of 3.6 Gm. per cent.

Disturbances in hepatic function as determined by the Bromsulphalein excretion test were noted in 11 patients. Dye retention correlated inversely with the severity of the congestive heart failure in these patients and hepatic function was noted to improve as signs of congestive heart failure cleared.

Hospital course

Upon selection for study, all patients were admitted for prolonged bed rest to a special research ward at the United States Public Health Service Hospital where appropriate diagnostic studies were undertaken. A period of prolonged complete bed rest was instituted with an objective of obtaining the maximum degree of reduction in heart size and improvement in the cardiac state of each patient. The total period of bed rest was determined by clinical response and modified by patient cooperation. It exceeded 12 months in 10 patients. In addition to conventional medi-

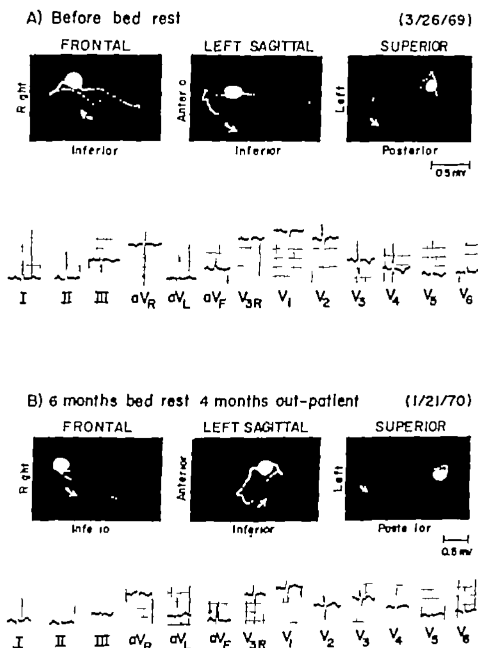


Fig 5 Vectorcardiograms and electrocardiograms of a 25-year-old Negro woman with postpartal cardiomyopathy The electrocardiogram (A) shows left ventricular hypertrophy and inverted precordial T waves which improved (B) after 6 months of bed rest and there was a return of the heart size to normal. The vectorcardiogram shows posterior and almost horizontal orientation of the QRS sÊ-loop with marked deformity of the loop which was somewhat less after bed rest.

cal therapy measures included bedside commode air conditioning bedside nursing care television radio and bedside occupational therapy

According to response to the therapeutic program of bed rest the 34 patients can be divided into five groups Group I 14 patients in whom all symptoms of cardiac disease subsided and the heart dimensions on x ray returned to normal Group II 7 patients in whom the symptoms of congestive heart failure improved and the heart size on x ray decreased but not to normal Group III 2 patients in whom the symptoms of congestive heart failure improved but in whom there was no reduction in heart size Group IV 5 patients who showed progressive deterioration of clinical status and died without ever leaving the hospital Group V 6 patients who for var

T ble IV *Response to bed rest of 34 patients according to duration of initial period of bed rest*

Response to bed rest	<50	50 to 100	100 to 150	150 to 200	200 to 250	250 to 300	300 to 350	350 to 400	400 to 450	450 to 500	>500	*Total*
	Days of bed rest											
	Prescribed period of bed rest completed (No. of patients)											
Heart size returned to normal	0	4	1	2	2	0	1	2	0	2	0	14
Heart size decreased but not to normal	0	1	1	0	0	1	0	0	1	1	2	7
Heart size did not decrease	0	0	0	0	0	1	0	1	0	0	0	2
Total	0	5	2	2	2	2	1	3	1	3	2	23
	Prescribed period of bed rest not completed (No. of patients)											
Progressiv congestive heart failure nd death in hospital	4	0	0	0	0	0	0	0	1	0	0	5
Left hospital	6	0	0	0	0	0	0	0	0	0	0	6
Total	10	0	0	0	0	0	0	0	1	0	0	11
Total all patients	10	5	2	2	2	2	1	3	2	3	2	34

ious reasons did not remain hospitalized for the prescribed period of bed rest.

The response of the 34 patients as related to the duration of bed rest is displayed in Table IV The average period of bed rest for all patients was 207 days. The duration of bed rest for patients in Group I varied from 78 to 491 days (average, 232 days) The average duration for Group II was 355 days (range 58 to 528 days) and for Group III was 349 days (range 255 to 427 days) The average periods of hospitaliza tion for patients in Groups IV and V were 104 and 19 days, respectively Although the success of treatment was not directly proportional to the length of bed rest (pa tients in Groups II and III generally tended to remain hospitalized longer than those in Group I) there were patients in whom re sponse to bed rest was slow and reduction in heart size did not begin until after 6 to 9 months of complete bed rest

In an attempt to categorize better those patients who were most responsive to bed rest in terms of reduction in heart size the total duration of heart disease prior to the institution of bed rest was compared in the five Groups (Table V) The average duration of illness for the patients in Group I was 3 months (range, 1 to 7 months) No patient with a duration of illness greater than 7 months experienced a return of heart size to normal. The average duration of illness for Group II was 22.5 months (vary ing from 3 to 56 months) and for Group III was 9 months (varying from 3 to 16 months) The average duration of illness for the patients who died while hospitalized (Group IV) was 26.5 months. The "de serters (Group V) averaged 2.5 months of illness prior to seeking medical treatment.

It is evident from these data that in an individual case the duration of symptoms of heart failure prior to treatment is an important prognostic factor as to the potential benefit to be derived from pro-longed bed rest.

The clinical course after institution of bed rest followed a general pattern with individual variations. In tially most pa tients demonstrated an unusual sensitivity to digitalis preparations as manifested by frequent and multifocal premature ventric ular contractions nodal mechanisms, and interference dissociation. Digitalis was or dered on a day by-day basis and potassium

Table X Response to bed rest of 34 patients compared according to the duration of illness prior to initial treatment with bed rest

Response to bed rest	Duration of heart disease before bed rest (months)									
	0 to 3	4 to 6	7 to 8	9 to 1	13 t 18	19 to 4	5 to 36	37 to 48	49+	Total
Heart size returned to normal	9	5	0	0	0	0	0	0	0	14
Heart size decreased but not to normal	1	2	0	0	1	0	1	1	1	7
Heart size did not decrease	1	0	0	0	1	0	0	0	0	
Progressive congestive heart failure and death in hospital	1	0	1	0	1	0	1	0	1	5
Left hospital before completing prescribed period of bed rest	5	0	1	0	0	0	0	0	0	6
Total	17	7		0	3	0	2	1		34

supplement or spironolactone was routinely used with mercurial diuretics The oral diuretics such as the thiazides and others predisposed to serious cardiac irregularities and therefore mercurial diuretics were used in all our patients Decrease in râles, in edema in hepatomegaly in venous distension and in orthopnea were usually the first manifestations of improvement The general appearance and health of the patients improved including their appetites The apical pansystolic murmurs became softer as heart size diminished and the intensity of the pulmonic second sound decreased The presystolic and protodiastolic gallop rhythms were the last abnormal physical signs to disappear These signs persisted indefinitely in some of the patients whose heart size did not completely return to normal The decrease in sensitivity to digitalis paralleled the reduction in heart size Cardiomegaly as measured by physical and radiographic examination was the last abnormal finding to recede (Figs 1 2 and 4) Electrocardiographic abnormalities persisted in almost all patients despite the decrease in cardiac size.

One may summarize the initial response to prolonged bed rest by stating that of 28 patients completing therapy one half (14 patients) showed return of heart size to normal (Figs. 1 and 2) one fourth (7 patients) showed improvement but persistence of some degree of cardiomegaly and one fourth (7 patients) failed to respond with any diminution in heart size (Fig 3)

There were five fatalities in this last group One was a 44-year-old Negro patient who had developed congestive heart failure 30 months previously following her tenth pregnancy She had been hospitalized for 4 weeks at Charity Hospital with symptomatic improvement Congestive heart failure recurred a year later following her eleventh pregnancy and again improved with a month's hospitalization with absolute bed rest after which she was followed as an outpatient Sixteen months later when referred to the bed rest program she was in profound electrolyte imbalance with hypokalemia hyponatremia azotemia and oliguria She died in intractable congestive heart failure on the tenth day of hospitalization

A 27 year-old Negro patient had developed congestive heart failure following her second pregnancy five years previously She responded to digitalis and diuretics but gradually discontinued her medications

as she felt better. After 2 months of gradually increasing symptoms she sought medical attention at Charity Hospital where marked cardiomegaly was noted. Upon referral to the Bed Rest Research Program she was given anticoagulants because of an episode of chest pain and hemoptysis and increasing signs of congestive heart failure. She exhibited unusual sensitivity to digitalis with ventricular ectopic activity. However there was no diminution in heart size with bed rest and she died quietly in bed on the thirty-sixth hospital day.

Another 30-year-old Negro patient developed congestive heart failure 2 weeks following delivery of a stillborn fetus, her eighth pregnancy and third stillbirth. Shortly thereafter she was admitted to the bed rest program, but after a month of intensive medical treatment she was still not free of symptoms of congestive heart failure. On the thirty-first hospital day she developed pleuritic chest pain and hemoptysis and died several hours later. Autopsy confirmed the presence of multiple pulmonary emboli.

A 34-year-old Negro patient developed congestive heart failure eight months previously and 20 weeks following the delivery of her fifth baby. Her congestive heart failure was never controlled despite 427 days of bed rest, and she died with complications of cerebral and pulmonary emboli.

The final hospital fatality was a 23-year-old Negro patient who developed congestive heart failure 18 months previously, 4 weeks following delivery of her third pregnancy. She was hospitalized for 6 weeks at Charity Hospital before returning to out-patient status on digitalis. A year later she again developed congestive heart failure following delivery of her fourth pregnancy. She was treated as an inpatient and outpatient of Charity Hospital for 4 months with incomplete response to therapy. During this time she experienced transient facial weakness and aphasia for which anticoagulants were administered. Following admission to the Bed Rest Research Program her congestive heart failure remained refractory and she died suddenly on the thirty-seventh hospital day.

Thus it can be seen that these patients without a beneficial response to bed rest characteristically had therapy instituted late in the course of their disease. In addition, embolic phenomena were present in 4 of the 5 patients who died.

Long term follow-up

Following discharge from the hospital the patients were seen at weekly or biweekly intervals in a cardiomyopathy clinic. Patients were readmitted for further periods of bed rest as indicated during subsequent pregnancies or by exacerbation of congestive heart failure, increase in heart size, and other medical problems.

The present status of the 34 patients is summarized in Table VI. Of the 14 patients in whom heart size initially returned to normal, 3 are dead and 1 has been lost to follow-up. Ten are living and 7 of these still have normal heart size (Fig. 2). Of the group who experienced a decrease in heart size but not to normal, 4 are living, 1 is dead, and 2 have been lost to follow up. One of the 4 living patients presently has a normal heart size. Of the two patients whose heart size did not decrease with bed rest, 1 is dead and 1 has been lost to follow-up. Of the 6 deserters, 2 are dead and 4 are living with normal heart size. The average duration of heart disease of these 4 survivors prior to entering the study was 3 months.

The present status of the patients as related to the duration of illness prior to entering the study is summarized in Table VII. The positive correlation of length of illness with the force of mortality is demonstrated by the average length of illness of 16 months in the deceased group as opposed to an average duration of illness of only 3 months in those patients who now have a normal heart size.

In addition to the 5 hospital deaths, there have been 7 other deaths in the series. Two deaths were among patients who could not remain hospitalized for the bed rest program. These two patients left the hospital after 5 and 23 days, respectively. Both died suddenly at home 2 and 6 months, respectively, after leaving the hospital. Two late deaths occurred in patients with incomplete response to bed rest.

Table VI. Present status of 34 patients grouped according to response to initial period of bed rest (mean follow-up 5 yr.)

Status	Group I: Heart size returned to normal with bed rest	Group II—Heart size decreased but not to normal	Group III—No decrease in heart size	Group IV—Progressive CHF & death in hospital	Group V: Left hospital before completing prescribed period of bed rest	Total
Living with normal heart size	7	1	0	0	4	12
Living with enlarged heart	3	3	0	0	0	6
Dead	3	1	1	5	2	12
Lost to follow-up	1	2	1	0	0	4
Total	11			5	6	34

Table VII. Present status of 34 patients compared with the duration of illness prior to bed rest

Status	Duration of illness before bed rest (months): 0 to 3	4 to 6	7 to 8	9 to 12	13 to 18	19 to 24	25 to 36	37 to 48	49+	Total
Prescribed period of bed rest completed (No. of patients)										
Living with normal size heart	5	3	0	0	0	0	0	0	0	8
Living with enlarged heart	2	3	0	0	1	0	0	0	0	6
Dead	3	1	0	0	0	0	1	0	0	5
Lost to follow-up	1	0	0	0	1	0	0	1	1	4
Prescribed period of bed rest not completed (No. of patients)										
Living with normal size heart	3	0	1	0	0	0	0	0	0	4
Dead	3	0	1	0	1	0	1	0	1	7

The initial hospitalization for 489 days of one 30-year-old patient was complicated by pulmonary emboli, and her heart size decreased but not to normal. She had two subsequent admissions for congestive heart failure a year and 2 years later and died during the second admission. Autopsy confirmed the presence of pulmonary infarcts. Another patient was initially hospitalized for 365 days with no decrease in heart size. She died at home 8 months later.

The other 3 deaths were among the group whose heart size returned to normal with initial hospitalization. One patient embarked on a program of a 16 hour work day coupled with grossly inadequate nutrition following discharge (Fig. 4). After 2 months of recurring symptoms of congestive heart failure, she developed acute pyelonephritis and died despite an additional 3 months of hospital care. Another patient returned to her home in a distant part of the state after 478 days of bed rest. She died suddenly at home 4 months later. The final death was in a 34-year-old patient who again developed cardiomegaly and symptoms of congestive heart failure 2½ years after discharge. During a brief hospitalization of 2 months she became asymptomatic and her heart size decreased but not to normal. Two years later a gradual increase in heart size was detected

without appreciable symptoms of cardiac disease. She refused to enter the hospital at that time and died at home several months later

In all, there have been a total of 16 additional admissions for control of congestive heart failure in 8 of the patients, three of which were terminal admissions in 3 patients who succumbed to their disease. One patient now lost to follow-up had four subsequent admissions for congestive heart failure. She left the hospital contrary to medical advice and has not been seen for 3 years. Efforts to locate her have been unsuccessful, and it is presumed that she is dead. Four patients now living with enlarged hearts have had a total of 9 subsequent admissions for recurrence of congestive heart failure

Subsequent pregnancies

The patients were studied to determine the effect of subsequent pregnancies on the clinical course of the disease and how this could be modified by bed rest. In 18 of the patients a total of 26 pregnancies occurred after the initial onset of congestive heart failure. Eleven of the pregnancies occurred prior to entering the study and 15 occurred after the patients had entered the bed rest program. The latter patients were admitted to the hospital and kept at bed rest from 4 months prior to delivery until 2 months post partum. From the 26 pregnancies there were 6 stillbirths, 3 among the 15 pregnancies in the bed rest group and 3 among the 11 pregnancies that occurred prior to bed rest. Exacerbations of congestive heart failure in the postpartal period occurred with 9 (88 per cent) of the 11 pregnancies not managed with bed rest. There were no exacerbations of congestive heart failure nor increase in heart size associated with the pregnancies of the 15 patients managed with bed rest. This experience attests to the deleterious effect of subsequent pregnancies on patients with cardiomyopathy through the increased stress imposed on an already diseased myocardium. In those patients in whom the myocardium was unloaded by complete rest in bed the added stress of pregnancy was tolerated without further decompensation. In addition to complete bed rest these patients also received careful attention as to diet and all other aspects of good medical care

Complications

Next to digitalis toxicity the most frequently encountered complication was that of pulmonary embolism. This occurred in 8 patients, 3 of whom suffered from concurrent thrombophlebitis of a lower extremity. There was an associated cerebral embolus in one of the patients with pulmonary emboli. Two other patients also experienced cerebral emboli. One patient suffered an embolus to the left superficial femoral artery. In most instances the initiation of thromboembolic phenomena preceded admission to the study and was not made worse by prolonged bed rest. Bed rest did not predispose to thromboembolic phenomena. Some patients admitted to the study were experiencing thromboembolic phenomena and continued to do so for 2 to 3 weeks after admission. Patients who had no thromboembolic disturbances prior to admission did not develop this complication when on the bed rest regimen

Acute pyelonephritis occurred in 4 patients. Two patients subsequently died and one has been lost to follow-up. The other is presently living with an enlarged heart and no evidence of renal disease.

Except for frequent premature ventricular contractions which were usually associated with digitalis therapy the only arrhythmias observed were episodes of atrial fibrillation in 2 patients. One occurred transiently during spinal anesthesia for gynecologic surgery in a patient whose heart size had returned to normal. The other occurred terminally in a patient who succumbed with intractable heart failure and pulmonary emboli. It is likely that the deaths, especially those which occurred suddenly, were due to fatal disturbances in cardiac rhythm. Salt restriction along with an oral diuretic, digitalis, physical stress, and other diseases seems to have predisposed to the serious disturbance in cardiac mechanism

Postmortem findings

Postmortem examinations have been performed in 8 of the 1[illegible] fatal cases. Signif[illegible]

cant findings were primarily limited to the heart

The *pericardium* was normal in all patients usually containing 10 to 60 ml of straw-colored fluid except in one patient in whom 600 ml of pericardial fluid were present In this patient there was a generalized anasarca with ascites and bilateral hydrothorax The myocardium was usually pale flabby and dilated In two cases grayish white plaques were present over the epicardium and in one instance areas of ecchymosis were noted over the atria

The heart weights varied from 41? to 670 grams (mean 531 grams) With the chambers open dilatation was more pronounced than an actual increase in wall thickness In fact the walls of the heart were rarely thick but the myocardial mass was increased The thickness of the free wall of the left ventricle varied from 0 4 to 2 9 cm (mean 1 5 cm) Right ventricular thickness ranged from 0 2 to 1 0 cm (mean 0 65 cm) Thickening of the endocardium was observed in 6 patients five of whom had pale fibrous plaques over portions of the ventricular endocardium These were most marked in the left ventricle but were observed in the right ventricle of 3 patients with associated uniform gray thickening of the left atrial endocardium The plaques involved both free and septal walls of the ventricles and were more prominent in the apical regions They varied from 0 5 to 4 cm in diameter and were 2 to 3 mm thick They did not involve the myocardium In two patients there were organized mural thrombi adherent to the sites of left ventricular endocardial thickening In one patient there was extensive calcification of one large plaque on the septal wall of the left ventricle This patient had developed pulmonary heart disease secondary to recurrent pulmonary embolization and demonstrated sclerotic plaques in the major pulmonary arteries

The circumferences of the mitral and tricuspid valves were increased proportionally to over all chamber dilatation There were no valvular calcifications or vegetations. In 1 patient there was fibrous thickening of the chordae tendineae of the mitral valve associated with adjacent endocardial fibrous plaques involving the papillary muscles. The coronary arteries were uniformly patent and entirely normal except for minimal sclerotic changes in several vessels

All patients exhibited chronic passive congestion of the lungs and intra-abdominal organs. Pulmonary infarction of recent origin was noted in 3 patients, and 2 patients had evidence of old infarction. Chronic passive congestion of the liver with central lobular necrosis was consistently observed Chronic bilateral pyelonephritis was noted in one subject.

Discussion

The literature contains conflicting reports as to the nature of or actual existence of postpartal cardiomyopathy as a distinct entity This report is not intended to clarify the pathogenesis of this cardiomyopathy but merely to present data on a group of patients fitting specific clinical criteria[4] which we feel comprise this entity

Much of the previous confusion may be clarified by a precise designation of the postpartal period It has been pointed out that existing heart disease made more manifest under the stress of pregnancy might comprise many of the reported cases.[19] It is also reasonable to assume that pregnant women are subject to the same spectrum of cardiovascular diseases as anyone else and that the stresses of pregnancy may augment the clinical severity of any type of myocardial disease present during the third trimester of pregnancy or shortly after delivery To illustrate this consider the original 27 patients reported by Hull and associates[6] Six of these patients developed congestive heart failure prior to delivery and 5 developed failure in the first week after delivery Of the total group he concluded that a third were suffering from the usual etiologic types of heart disease Similarly of the 15 patients reported by Meadows,[14] 2 developed heart failure prior to delivery and 2 developed failure more than 4 months following delivery The other 11 were described as having developed failure within 3 months after delivery although the exact period of time that elapsed following delivery in the individual cases is not specified Although designated as postpartal heart disease

many of the case reports compiled from the literature describe heart failure actually preceding delivery. Others have used similar broad criteria but term the occurrence of heart failure in this setting "peripartal" heart disease.[2, 7] However, the importance of an asymptomatic period for several weeks following delivery in separating postpartal cardiomyopathy from other types of heart disease was recognized by early observers of this type of cardiomyopathy.

Thus, in the present study, in order to exclude those patients with occult or unidentified pre-existing myocardial disease or with any type of heart disease which was superimposed upon a pregnancy, the criteria for "postpartal" heart disease required that patients have normal heart size on x-ray, normal electrocardiogram, and be free of signs and symptoms of heart disease prior to and during pregnancy as well as for 2 weeks following delivery, that is, there had to be no evidence of heart disease during or shortly after pregnancy. Patients in whom heart disease developed more than 20 weeks after delivery were also excluded. The use of these criteria and the exclusion of those patients in whom a specific etiology of the heart disease could be established allowed a characteristic clinical picture to emerge which can be described as follows: A young multiparous woman with a strong family history of heart disease, a long history of marginal nutrition, and a likelihood of previous abortions, stillbirths, or "toxemia" undergoes an uneventful delivery. Between 2 and 20 weeks later she experiences the rather abrupt onset of symptoms of left ventricular failure. After delaying several weeks, she seeks medical attention, at which time signs of right ventricular congestive heart failure are evident. In addition to the signs of congestive heart failure, evaluation reveals generalized cardiomegaly, diffuse electrocardiographic abnormalities, a propensity to digitalis intoxication, and a significant incidence of thromboembolic phenomena. This patient has a typical clinical pattern of cardiomyopathy which develops with no apparent cause between 2 weeks and 20 weeks of an apparently normal delivery.

If treatment is instituted early, symptomatic response is prompt, and if bed rest is continued, a return of heart size to normal may be anticipated in most patients. The longer treatment is delayed, the less likely is a favorable clinical response. Premature curtailment of bed rest, resumption of undue physical exertion, return to previous dietary habits, and subsequent improperly managed pregnancies are associated with exacerbations of heart disease with less optimal response to treatment than initially. Undue delay in treatment or continued cardiac enlargement with exacerbation of heart failure indicates a poor prognosis.

Although the precise pathogenesis of postpartal cardiomyopathy is yet to be established, some practical clinical points emerge from the careful follow-up of these patients. The benefit of prolonged bed rest in the management of these patients is shown by the fact that of the 28 patients who cooperated in the bed rest program, 14 experienced a return of heart size to normal. Of further importance is the value of instituting bed rest early in the course of the disease. Of the 19 patients who entered the bed rest program within 6 months of the onset of their disease, 14 experienced a return of the heart size to normal. Of the 9 patients in whom bed rest was instituted six or more months after the development of heart disease, none regained normal heart size. However, 5 experienced symptomatic improvement and in 4 a limited decrease in heart size did occur. Also of interest in this light are the 6 patients who deserted the bed rest program. Medical management was continued on an out-patient basis and heart size returned to normal in 4 of these patients. Each of these 4 patients had a duration of illness of less than three months at the time their therapy was initiated. In the long-term follow-up the obvious effect of duration of disease prior to the institution of therapy on the over-all force of mortality was apparent (Table VII). The disparity between the high mortality rate noted in the initial cases and the mortality figure represented in the present data demonstrates the effect of an increased awareness of this type of cardiomyopathy and the earlier institution of therapy.

Once maximal benefit from bed rest has been achieved it is essential that proper rest diet and medical therapy be continued forever if possible following discharge from the hospital Of the 7 deaths that occurred after the initial hospitalization four were associated with a deviation from the therapeutic regimen

The deleterious effect of subsequent pregnancies on patients with postpartal cardiomyopathy is shown by the exacerbations of congestive heart failure during 9 of 11 pregnancies not managed with bed rest The beneficial modifying effect of bed rest is evident from the fact that 15 pregnancies were so managed without an exacerbation of congestive heart failure Nevertheless we consider postpartal cardiomyopathy a medical contraindication to further pregnancies and advise sterilization procedures in these patients

At present the etiology of postpartal cardiomyopathy is purely conjectural Suggested factors include immune responses to fetal tissue nutritional deficiencies viral infections endocrine imbalance and autoimmunity to the muscle products of the rapidly involuting uterus[14] Striking features among our patients were the prevalence of poor dietary habits multiparity and obstetrical complications The unusual incidence of sickle cell hemoglobin (AS) and hemoglobin C trait (AC) may have pathogenic significance but exactly what the significance is awaits explanation The possibility of the stress of normal pregnancy alone causing cardiomyopathy is still a very real one Answers to these questions of pathogenesis and etiology will only be obtained by further study

Summary

Thirty four patients selected to meet specific clinical criteria for postpartal cardiomyopathy were studied Nutritional and obstetrical histories were evaluated along with a thorough diagnostic work up including radiographic electrocardiographic and vectorcardiographic studies

Treatment with prolonged complete rest in bed was instituted and supplemented with conventional medical therapy The response to this program of therapy has been evaluated as well as the effects of subsequent pregnancies and deviations from the therapeutic regimen A sensitivity to digitalis preparations and a relatively high incidence of thromboembolic phenomena have been observed in postpartal cardiomyopathy However the latter was not due to bed rest but rather to the cardiac disease state

The study of these cases discloses a fairly characteristic clinical picture of postpartal cardiomyopathy However pathologic study of 8 of the cases has revealed no specific diagnostic features. The importance of the early institution of therapy especially complete bed rest, in altering the otherwise poor natural course of the disease is emphasized.

REFERENCES

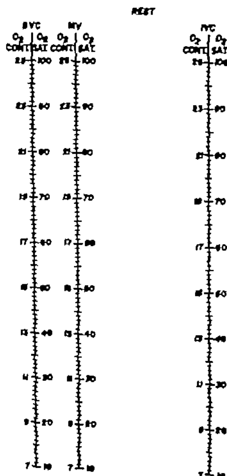
1 Meadows, W R. Postpartum heart disease, Amer J Cardiol 6:788, 1960.
2 Stuart, K. L. Cardiomyopathy of pregnancy and the puerperium Quart. J Med. 37:463, 1968
3 Herrmann, G R. and King B. L. Cardiovascular disturbances in the obstetric patient, J A.M.A. 9 :1472 1930
4 Hull E. and Hafkesbri g [Hafkesbring] E. Toxic postpartal heart disease New Orleans Med Sci J 89:550, 1937
5. Hull E. and Hidden, E. Postpartal heart failure, Southern Med J 31:265 1938.
6. Musser J J Sodeman, W A., and Turner R. J Heart failure or acute nephritis with onset about 3 weeks after delivery Ann. Intern. Med. 1[illegible]:739 1938.
7 Musser J J and Sodeman, W A. Heart changes of unusual etiology in pregnancy Trans. Ass. Amer Physicians 54:181 1939.
8. Sodeman, W A. Cardiac changes in pregnancy as related to the usual etiological types of heart disease AMER. HEART J 19:385 1940.
9 Bashour F and Winchell P Post partal heart disease—A syndrome? Ann. Intern Med. 40:803 1954
10. Brown A. K Doukas, N Riding W D and Jones, E. W Cardiomyopathy and pregnancy Brit. Heart J 29:387 1967
11 Walsh, J J Burch G. E. Black, W C. Ferrans, V J and Hibbs, R. G. Idiopathic myocardiopathy of the puerperium (postpartal heart disease) Circulation 32 19 1965
12 Burch G. E., Walsh J J and Black, W C.: Value of prolonged bed rest in management of cardiomegaly J.A M.A. 183:81 1963.
13 Burch G. E. and Hyman, A : Influence of hot and humid environment upon cardiac output and work in normal man and in patients with chronic congestive heart failure at rest, AMER. HEART J 53:665 1957
14 Burch, G. E. and Hyman, A : Study of influence of tropical weather on output of volume,

work, and power by right and left ventricle of man at rest in bed, AMER. HEART J. 57:247 1959

15. Sanders, V. Idiopathic disease of the myocardium, Arch. Intern. Med. 112:75 1963.
16. Meadows, W. R. Idiopathic myocardial failure in the last trimester of pregnancy and the puerperium, Circulation 15:903 1957
17. Stuart, K. L. Peripartal cardiomyopathy Cardiologia 52:44, 1968.
18. Burch G. E., and DePasquale, N. P., Heart muscle disease, D M M y 1968.

Erratum

In the article entitled Nomograms for determination of mixed venous oxygen content and oxygen step-up in atrial septal defect, by J. Douglas Ridges, M.D. and Donald C. Harrison, M.D. which appeared on pp. 575-576 of the October 1970, issue of the JOURNAL, Fig. 1 is incorrectly presented. The space between the "MV" column and the IVC" column is insufficient. Fig. 1 is presented correctly here.



The effects of glucagon on sodium, potassium, and urine excretion in patients in congestive heart failure

*Juris Simanis M.D.**
Leon I. Goldberg Ph.D. M.D.
Atlanta, Ga.

The hyperglycemic pancreatic hormone glucagon has recently received considerable attention as a positive inotropic agent. Farah and Tuttle[1] reported in 1960 that glucagon increased cardiac contractility and heart rate of isolated hearts of several species of animals. The suggestion that the agent may have a role in the treatment of myocardial failure was made in 1968 by Lucchesi[2] and Glick and associates. These investigators independently reported that glucagon increased myocardial contractility of both intact and isolated animal hearts despite prior administration of a beta-adrenergic blocking agent. Later in the same year Parmley and co-workers[4] and Klein and associates[5] demonstrated that intravenous administration of 3 to 5 mg. of glucagon increased myocardial contractility and cardiac output of normal subjects and patients with heart disease. Arrhythmias were not observed and the actions of glucagon did not appear to be affected by concurrent treatment with digitalis. Other investigators have now confirmed the positive inotropic effect of glucagon in man[6,7] and the hormone has been administered to patients with acute and chronic heart failure with varying results.[8-15]

We initiated the present study to determine whether glucagon would cause a beneficial diuresis in patients with chronic congestive heart failure.

Methods

Glucagon for injection (United States Pharmacopeia, Eli Lilly & Co.) was dissolved in the accompanying diluting fluid and administered by intravenous injection in a concentration of 1 mg. per milliliter or by intravenous infusion after dilution with 5 per cent glucose in water. The hormone was administered to 12 patients with congestive heart failure. All patients were designated as functional Classes II to IV according to the New York Heart Association classification. The first 4 patients were studied to determine the maximum tolerated dose of glucagon and the most appro-

From the Department of Medicine (Division of Clinical Pharmacology) and the Medical Services of Grady Memorial Hospital, Emory University School of Medicine, Atlanta, Ga.
This investigation was supported in part by Grants HE 06491, GM 14270, and FR 39 from the National Institutes of Health.
Received for publication May 5, 1970.
Reprint requests to: Dr. Leon I. Goldberg, Department of Medicine, Emory University School of Medicine, 69 Butler Street S.E., Atlanta, Ga. 30303.
*Dr. Simanis was supported by a postdoctoral fellowship in Clinical Pharmacology from the National Institutes of General Medical Sciences (GM 01543).

Table I. Doses and times of glucagon and dopamine administration

Patient	Diagnosis	Glucagon											Dopamine	
		1st injection			2nd injection				3rd injection					
		Dose (mg.)	N	V	Dose (mg.)	N	V	Time (min.)	Dose (mg.)	N	V	Time (min.)	Maximum infusion rate (μg/Kg/min.)	Time† (min.)
W. H.	Hypertensive heart disease	5	0	0	7.5	0	0	15	10	0	0	130	2	−15
E. C.	Coronary heart disease	5	+	0	5	+	0	15	5	+	+	70	1	250
V. L.	Hypertensive heart disease	5	+	0	3	+	0	15	3	+	0	60		−30
S. B.	Unknown	5	+	0	5	+	+	70	3	+	+	100	5	−30
L. C.	Hypertensive heart disease	5	0	0	5	0	0	15	7.5	0	0	70	5	145
T. M.	Unknown	5	+	0	4	+	+	30	5	+	+	60		
J. B.	Cardiomyopathy	5	0	0	5	+	+	20	4	+	+	60		
M. P.	Unknown	5	0	0	5	+	+	20	4	+	+	60	3	295
J. B.		5	+	0	3	0	0	30	3	0	0	30		
M. P.		5	0	0	4	0	0	30	4	0	0	30	3	245

N = Nausea. V = vomiting.
*After administration of spironolactone, 25 mg., four times a day for 3 days.
†Minutes before (−) or after first glucagon injection.

priate method of administering the drug. Urine flow before and after glucagon injections was measured as described below. On the basis of these preliminary data, the next group of 8 patients was studied more intensively—7 patients in the Emory University Clinical Research Facility and one in the Intensive Care Unit of Grady Memorial Hospital. The presumed etiologies of the heart failure in these patients are shown in Table I. Glucagon was injected intravenously over a 30 to 60 sec. interval. Initial doses were 5 mg. and subsequent doses were determined by the status of the patients. Five patients also received an intravenous infusion of dopamine (Intropin, Arnar-Stone Labs., Inc.) after administration of glucagon; one patient received dopamine before glucagon was administered. The rate of the dopamine infusion was increased until a noticeable increment in urine flow was obtained. Doses of glucagon and dopamine and times of administration are shown in Table I.

Food was withheld for at least 12 hr. before and during the study. Maintenance doses of digitalis were given on the day of the study in some patients. However, diuretics and other medications were discontinued at least 24 hr. prior to the investigation. Water was administered orally each hour to insure adequate urine flow. Urine was collected during periods of approximately 30 min. through an indwelling Foley catheter, and each collection was terminated with multiple air washes to assure complete collection. Two 30 min. urine collections were made prior to the injection of glucagon. Sodium, potassium, and creatinine were measured in each aliquot. The values obtained during the two periods prior to glucagon infusion were averaged. Venous blood samples were collected prior to and one hour after the first glucagon injection and several hours after the last glucagon injection for the determination of serum sodium, potassium, and creatinine. The percentage of filtered load of sodium or potassium was obtained by dividing the clearance of sodium or potassium by the creatinine clearance. These measurements were previously used by

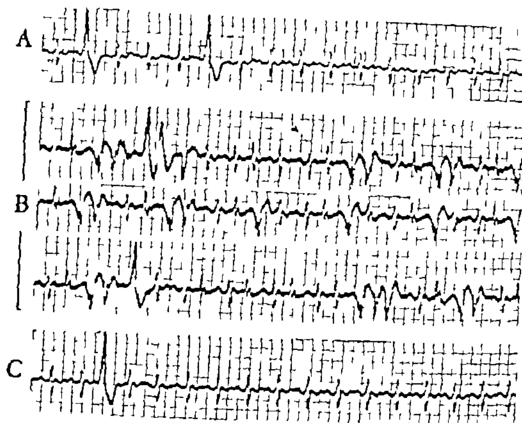


Fig 1 Electrocardiographic tracings (Lead III) obtained from E. S age 59 before and after glucagon infusion. A Tracing obtained before beginning infusion. B Continuous recording showing arrhythmia which occurred 20 min. after the glucagon infusion was begun The patient complained of nausea and vomiting 2 min. before this tracing was obtained and the infusion was discontinued The patient received a total of 4 5 mg. of glucagon. C, Tracing shows return of electrocardiogram to control pattern. The duration of the arrhythmia was about 3 min. Antiarrhythmic drugs were not given

Elrick and co-workers[14] in a study of the effects of glucagon in normal subjects. Blood pressure was recorded by sphygmomanometer every 5 to 10 min and the electrocardiogram was monitored continuously Statistical comparisons were performed by the paired t test

Results

Preliminary studies Glucagon was administered by intravenous infusions to 2 patients In the first patient an infusion of 4 5 mg during a 40 min period resulted in nausea and vomiting and reduction in urine flow In the second patient an intravenous infusion of 4 5 mg of glucagon over a 13 min period was followed by an increase in urine flow from 0 47 to 0 63 ml per minute During the infusion of glucagon the patient experienced severe nausea and vomiting the electrocardiogram which initially showed atrial flutter with 2 1 block and occasional premature ectopic beats began to exhibit multifocal ventricular ectopic beats and short runs of ventricular tachycardia (Fig 1) The infusion of glucagon was immediately discontinued The ectopic activity persisted for 2 to 3 min After this period the electrocardiogram reverted to the rhythm and pattern observed during the control period Except for nausea and vomiting the patient did not complain of other symptoms and the remainder of his hospital stay was uneventful Because of these untoward experiences with intravenous infusions glucagon was administered by rapid intravenous injections in doses of 2 to 4 mg to 2 other patients. Urine flow increased transiently after 3 of such injections

In view of the difficulties obtained with intravenous infusions of glucagon and the transient diuresis produced by a single intravenous injection subsequent patients received 3 injections of glucagon at intervals shown in Table I

Table II Effects of glucagon and dopamine on sodium and potassium excretion and urine flow

Drug	W H	E C	N L	S B	I C	T M	J B	M P	(Mean)	J B	M P
					µEq of sodium excreted/min.						
Control	136.7	122.9	161.9	144.0	20.4	3.7	4.5	84.4	84.8	30.7	103.2
1st Injection	312.6	335.1	395.7	393.5	60.3	4.7	5.0	176.5	210.4	28.7	189.4
2nd Injection	358.3	311.9	173.9	207.5	176.3	12.5	3.2	71.7	226.9	12.9	137.6
3rd Injection	325.8	356.8	172.6	213.7	115.3	8.7	3.8	44.9	155.2	16.2	133.8
Dopamine	1852.7	336.8	781.2	197.3	569.0			273.0	663.3		364.1
					Filtered load sodium excreted (%)						
Control	1.38	1.18	0.96	0.87	0.51	0.07	0.09	1.02	0.76	0.56	1.50
1st Injection	2.94	2.91	1.93	2.24	0.93	0.08	0.08	1.93	1.64	0.52	1.95
2nd Injection	5.37	2.35	0.96	1.31	1.80	0.15	0.10	1.10	1.64	0.28	1.76
3rd Injection	2.60	2.07	0.98	1.68	1.73	0.16	0.08	0.60	1.24	0.33	1.66
Dopamine	14.56	2.70	4.28	1.24	5.63			2.52	5.05		3.22
					µEq of potassium excreted/min						
Control	3 44	23.8	21.3	18.5	14.1	24.4	61.2	35.2	29.1	50.1	26.8
1st Injection	49.4	55.1	30.7	42.6	24.1	30.2	80.6	59.9	46.6	61.0	55.4
2nd Injection	67.6	43.8	19.4	26.0	39	40.5	38.4	34.8	38.8	43.6	45.5
3rd Injection	35.2	72.4	19.5	36.6	29.4	29.4	50.0	37.2	41.2	43.0	43.7
Dopamine	80.6	31.9	38.8	34.0	57.1			51.2	56.3		44.4
					Filtered load potassium excreted (%)						
Control	11.6	7.2	4.2	5.0	14.1	12.4	35.2	16.6	13.3	27.3	13.4
1st Injection	16.6	16.1	5.16	11.6	17.9	15.8	41.6	25.8	18.6	32.4	25.4
2nd Injection	15.5	11.7	4.0	13.6	20.7	15.2	44.3	20.2	16.6	29.5	22.7
3rd Injection	10.7	14.0	4.24	13.2	23.1	15.0	29.1	18.1	15.9	27.1	21.3
Dopamine	21.8	11.8	10.0	10.0	27.7			18.4	16.6		14.6
					Urine flow ml./min						
Control	1.23	1.48	2.90	1.22	0.39	0.41	1.02	2.51	1.40	1.22	2.40
1st Injection	2.47	1.97	7.69	4.73	0.46	0.45	1.26	3.33	2.80	1.22	3.08
2nd Injection	6.77	1.76	4.91	2.1	1.20	0.88	0.63	0.81	2.39	0.86	1.98
3rd Injection	2.78	2.04	1.50	1.33	0.84	0.62	0.84	0.51	1.31	0.90	1.90
Dopamine	19.80	8.25	7.45	4.12	4.95			8.53	8.85		8.88

After administration of spironolactone, 25 mg four times a day for 3 days.

Detailed studies The effects of glucagon and dopamine on urinary sodium and potassium excretion and urine flow in the 8 patients in whom quantitative studies of electrolyte excretion were carried out are shown in Table II Each patient exhibited an increase in sodium excretion during the 30 min period following the initial injection of 5 mg of glucagon The urinary excretion of sodium increased from an average of 84.8 µEq per minute to 210.4 µEq per minute ($p < 0.01$) The percentage of filtered load of sodium increased from an average of 0.76 to 1.64 per cent ($p < 0.01$) An additional increase in sodium excretion occurred in 3 patients in the period following the second injection of glucagon After the third injection of glucagon, only one patient excreted more sodium than during the second injection and in fact, 4 of these patients excreted less sodium after the third injection than after the first injection Sodium excretion did not increase in any of the patients during the subsequent 60 to 180 min and urinary sodium excretion rates less than control were recorded during at least one 30 min. period in 7 of the 8 patients. In general, changes in urine flow and potassium excretion paralleled the changes in sodium excretion (Table II) The magnitude and duration of the changes in urine flow and electrolyte excretion produced by two 5 mg injections and one 4 mg injection of glucagon in Patient M P are shown in Fig 2 Sodium excretion increased only after the first injection, Nausea

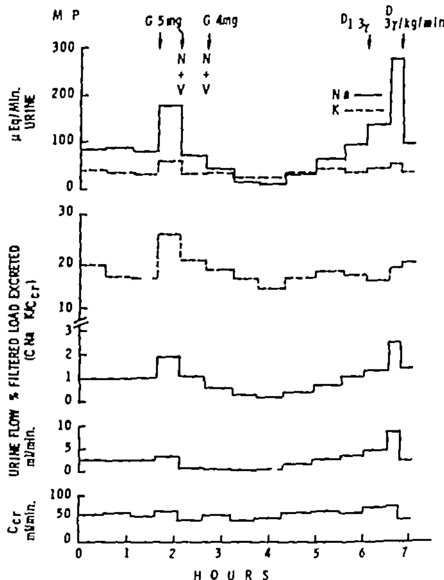


Fig 2 1 Effect of intravenous i jections of glucagon and an intravenous infusion of dopamine on sodium and potassium excretion, urine flow nd creatinine clearance in Patient M P *N* and *V* signify the occurrence of nausea and vom ting after the second and third injection of glucagon.

and vomiting occurred after both the second and third injections and the natriuresis was not maintained During the next 60 min less sodium was excreted than during the control period Dopamine was admin istered 4 hr after the third injection and sodium excretion and urine flow markedly increased

Administration of glucagon was repeated in 2 patients (M P and J B) after treat ment with spironolactone in a dose of 25 mg 4 times a day for 3 days The levels of potassium excreted were lower and the levels of sodium excreted were higher after administration of spironolactone in each patient (Table II)

The changes produced by glucagon during spironolactone therapy in Patient M P are shown in Fig 2B The magnitude of the natriuresis following the initial injection of glucagon was similar in studies before and during spironolactone therapy During spironolactone therapy this patient did not vomit and electrolyte excretion increased following the second and third injections of glucagon Spironolactone treatment did not improve the response to glucagon in Patient J B

Blood glucose levels increased in all patients following glucagon administration The average control blood glucose value was 112 2 mg per cent. One hour following

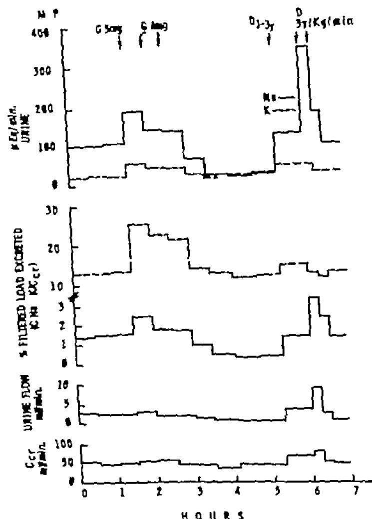


Fig. 2B. Effects of glucagon and dopamine in Patient M. P. after administration of spironolactone, 25 mg. four times a day for 3 days. The second dose of glucagon was reduced to 4 mg. and the patient did not experience nausea or vomiting.

the first injection of glucagon the average value of blood glucose was 155.8 mg. per cent ($p < 0.001$). Only one patient, E. C. developed transient glycosuria with the glucagon-induced hyperglycemia. Serum potassium decreased in all patients from a mean control value of 3.90 mEq. per liter to 3.65 mEq. per liter one hour after the first glucagon injection ($p < 0.001$). Serum sodium decreased in 5 of the 8 patients. The mean control value was 137.2 mEq. per liter; one hour after the first glucagon injection the value was 135.0 mEq. per liter ($p < 0.05$). A significant change in serum calcium did not occur.

The incidence of nausea and vomiting after each injection of glucagon is shown in Table I. There was no consistent correlation between the occurrence of nausea and vomiting and changes in sodium excretion.

Changes in blood pressure and heart rate following glucagon injections were extremely variable, particularly in patients experiencing nausea and vomiting. There was no consistent relationship between these measurements and sodium excretion.

Effects of dopamine. The effects of dopamine are shown in Table II. Sodium excretion and urine flow increased during each

dopamine infusion Increments were greater than those occurring with glucagon in 4 of 6 patients. The dose of dopamine was adjusted so that minimum changes in heart rate and blood pressure occurred The infusion rate was increased slowly until detectable increments in urine flow were observed and then maintained at that rate The maximally effective dose of dopamine was not sought

Results of subsequent therapy Six of the 8 patients had significant diuresis and symptomatic improvement after a regimen of bed rest digitalis thiazide diuretics and low salt diet One patient I C needed more vigorous therapy with furosemide. Patient J B who had practically no response to glucagon also failed to respond to other therapeutic measures and died 13 days after the investigation The autopsy revealed idiopathic myocardiopathy with mural thrombi in all cardiac chambers

Discussion

The present study demonstrated that intravenous injections of glucagon produced a statistically significant increase in sodium excretion in patients with congestive heart failure This effect was transient however and appeared to be of little clinical significance despite repeated injections of the hormone.

Although most of the recent studies of glucagon have emphasized its cardiac effects, the hormone also exerts actions on the kidney which could account for the transient natriuresis. In 1959 Elrick and associates[16] reported that intravenous injections of glucagon produced significant but transient increments in sodium potassium and chloride excretion in normal subjects. An action of glucagon on the renal tubule was proposed since changes in creatinine and inulin clearance bore no relationship to the electrolyte response The increases in the filtered load of sodium and potassium which occurred in most of our patients in congestive heart failure were similar in magnitude and duration to those occurring in studies of normal subjects by Elrick and co-workers[16] suggesting that the mechanisms are the same in both states. Further evidence for a renal action is provided by dog studies in which administration of glucagon intravenously[17] and into a renal artery[11,21] produced natriuresis without increasing glomerular filtration rate

The question may be raised that glucagon did not produce a greater diuresis because of a totally unresponsive state of our patients However infusions of dopamine produced increments in sodium and urine excretion[19] in each of 6 patients and conventional therapy was effective in causing significant weight loss and clinical improvement in all but one of our patients. Unfortunately the one patient, J B who did not respond to conventional medications also did not respond to glucagon The treatment of this unresponsive patient and one of the other patients with spironolactone did not increase the effectiveness of glucagon. Recent investigations by Amsterdam and co-workers[13] and Vander Ark and Reynolds[14] suggest that glucagon may not exert beneficial hemodynamic effects in patients with chronic congestive heart failure The former investigators reported that intravenous administration of glucagon in doses of 50 µg per kilogram increased cardiac index an average of only 0 7 L. per minute per square meter in patients with congestive heart failure Heart rate blood pressure left ventricular end diastolic pressure and systemic vascular resistance were not altered The latter investigators reported that intravenous infusions of glucagon did not produce clinical improvement in patients with chronic congestive heart failure who were maintaining a reasonable blood pressure Poor response in patients with chronic congestive heart failure may be related to inability of the failed myocardium to respond to glucagon Levey and co-workers[22] reported that glucagon did not increase right ventricular papillary muscle contractility in cats with chronic isolated right ventricular failure. They also found that glucagon did not increase adenyl cyclase in particulate preparations obtained from both right and left ventricles of these cats as it did in preparations from normal cats.

Despite these discouraging results, continuous administration of glucagon at a low infusion rate could conceivably cause a diuresis in some patients by impairing sodium reabsorption by the kidneys. Bro-

gan and associates[11] reported that infusions of glucagon at a rate of 2 mg per hour for 9 days resulted in a 25 lb. weight loss and "marked temporary improvement in a terminally ill patient who gained weight on conventional therapy These investigators also reported that a second severely ill patient lost 11 lb when glucagon was infused for 10 days at rates ranging downward from 5 to 1 mg per hour Both these patients were hyponatremic, however and water restriction and reduction of the previous diuretic regimen were instituted either shortly before or simultaneously with the glucagon therapy

Finally it is important to be aware of possible hazards of administering glucagon to patients with chronic congestive heart failure Glucagon increases transmission through the A V node[23, 24] and could thereby increase the ventricular rate of patients with atrial fibrillation. A more serious occurrence would be the initiation of potentially fatal ventricular arrhythmias as occurred in one of our patients. Several investigators have concluded that glucagon differs from other cardiac stimulants in that its positive inotropic action is not accompanied by increased ventricular irritability [4,24,25] Recently however Lipski and co-workers[26] reported that ventricular premature contractions and ventricular tachycardia followed glucagon injections in the anesthetized dog Regardless of which of these conclusions is correct vomiting could initiate arrhythmias in a patient with limited cardiac reserve. On this basis we feel that the previously held contention that the side effects of glucagon are benign is no longer tenable

Summary

The effects of 3 intravenous injections of glucagon on sodium potassium and urine excretion were determined in 8 patients with chronic congestive heart failure. Initial injections of 5 mg of glucagon resulted in statistically significant average increments in sodium excretion from 84.8 to 210.4 μEq per minute in potassium excretion from 0.7 to 1.6 μEq per minute and in urine flow from 1.4 to 2.2 ml per minute Second and third injections of glucagon (3 to 10 mg) sustained the natriuresis in only 4 patients. Six patients experienced nausea and 5 patients vomited thus preventing the use of larger doses of glucagon One patient, in a preliminary study in which glucagon was infused intravenously developed a short episode of multifocal ventricular tachycardia shortly after vomiting occurred. Because of the relatively limited diuresis and nausea and vomiting we conclude that single injections of glucagon in doses used in this study did not offer advantages over existing methods of treatment in our patients.

We are indebted to the house staff of Grady Memorial Hospital for referral of these patients. We also wish to thank Dr F G. Henderson of the Lilly Laboratory for Clinical Research, of Indianapolis, Ind., for supplies of glucagon and Dr Kane Zelle of the Arnar Stone Labs Inc., in Mt. Prospect, Ill., for supplies of injectable dopamine (Intropin, Arnar Stone Labs Inc.)

REFERENCES

1 Farah, A., and Tuttle, R.: Studies on the pharmacology of glucagon, J Pharmacol. Exp. Ther 129:49 1960.
2 Lucchesi, B R. Cardiac actions of glucagon, Circ. Res. 22 777 1968.
3 Glick, G., Parmley W W Wechsler A.S and Sonnenblick, E. H. Glucagon, its enhancement of cardiac performance in the cat and dog and persistence of its inotropic action despite beta receptor blockade with propranolol, Circ. Res. 22 789 1968
4 Parmley W W Glick, G., and Sonnenblick E. H. Cardiovascular effects of glucagon in man, New Eng. J Med. 279 12, 1968.
5 Klein, S. W Morch J E., and Mahon, W A. Cardiovascular effect of glucagon in man Canad. Med. Ass. J 98 1161 1968.
6 Williams, J F Childress, R. H Chip, J N and Border J F Hemodynamic effects of glucagon in patients with heart disease, Circulation 39:38, 1969
7 Linhart, J W Barold S. S., Cohen, L. S. Hildner F J and Samet, P Cardiovascular effects of glucagon in man, Amer J Cardiol 22 706, 1968.
8 Parmley W W Matloff J M and Sonnenblick, E. H. Hemodynamic effects of glucagon in patients following prosthetic valve replacement, Circulation 39 155 1969
9 Gregory J Moeller H., Gool J Ayres, S Giannelli, S., and Conklin, E. Effects of glucagon on cardiovascular dynamics and myocardial metabolism in the low output state Clin. Res. 17:241, 1969 (Abst.)
10 Mahon W A., Morch, J E., and Klein, S. W Cardiovascular effects of intravenous glucagon in man, Circulation 38 132 1968. (Abst.)
11 Brogan, E Kozonis, M C., and Overy D C.

Glucagon therapy in heart failur Lancet 1:182 1969

12 Greenberg B H McCall ter B D and Lrve R C Hemodynamic effect of glucagon in patients with coronary artery disease at rest and during mild upine exercise Clin. Res. 1 :443 1969 (Abst)

13 Amsterdam L A Zelis R Spann J F Hurley F J and Mason D T Current statu of glucagon in cardiac pump failure hemodynamic result and comparison with catechol amines Clin Res. 18:295 1970

14 Vander Ark C P and Reynold I W Clinical evaluation of glucagon by continuou infu ion in the treatment of low cardiac output tates, Amer Heart J 79:181 1970

15 Lkkly J D O Brien I T and Sulgh S P Glucagon and haemodynamics of acute myocardial nfarction Brit Med J 1:663 1969

16 Elrick L Huffman F K Hlad C J Whipple N and St ub, A Effect of glucagon on renal function in man J Clin Endocrinol 18:279 1955

17 Staub, A Springs A Stoll F and Elrick H A renal action of glucagon Proc Soc Exp. Biol Med 94:57 1957

18 Pullman T N Lavender A R and Aho, I Direct effect of glucagon on renal hemodynamics and excretion of inorganic ions Metabolism 16:358 1967

19 Stowe N T and Hook J B Alterations in renal hemodynamics a possible mechanism of the natriuretic action of glucagon The Pharmacologist 10 163 1968 (Abst)

20 McDonald R. H Jr Goldberg L I McNa J L and Tuttle L P Effects of dopamine in man augmentation of sodium excretion, glomerular filtration rate and renal plasma flow J Clin. Invest. 43:1116 1964

21 Levey G S Prindle K H and Epstein, S E Effects of glucagon on adenyl cyclase activity in the left and right ventricles and liver in experimentally produced isolated right ventricular failure Clin. Res. 18:317 1970 (Abst)

22. Whitsitt L S and Lucchesi, B. R. Effects of beta receptor blockade and glucagon on the atrioventricular transmission system in the dog, Circ Res. 23:585 1968

23 Steiner C Wit A L, Berkowitz W D Lau, K L, Weiss M B Rosen, W D Lau, S H and Damato, A N The effect of glucagon on atrioventricular conduction in man, Clin. Res 1 :265 1969 (Abst)

4 Steiner C Wit A C and Damato, A N Effect of glucagon on atrioventricular conduction and ventricular automaticity in dogs, Circ Res. 24:167 1969

5 Lucchesi B R Stutz D R and Winfield, R A Glucagon Its enhancement of atrioventricular nodal pacemaker activity and failure to increase ventricular automaticity in dogs Circ Res. 25:183 1969

26. Lipski, J I Kaminsky D M Donoso, E and Friedberg C K The electrophysiologic properties of glucagon on the normal canine heart Amer J Cardiol 23:124 1969 (Abst)

Experimental and laboratory reports

Changes in norepinephrine stores in the canine heart following experimental myocardial infarction

Peter Mathes M.D
Sigmundur Gudbjarnason Ph.D
Detroit Mich

Previous studies have shown that patients as well as experimental animals show an elevated plasma level and increased urinary excretion of norepinephrine (NE) following myocardial infarction.[1-4] These changes have been attributed to an augmented activity of the sympathetic nervous system and the elevated plasma norepinephrine levels are thought to maintain blood pressure and to stimulate the myocardium directly forming a protective reaction to prevent shock and cardiac decompensation.

Following coronary artery occlusion norepinephrine is released from the ischemic tissue into the circulation and the infarcted tissue shows a marked decrease in norepinephrine content.

In previous studies from this laboratory it has been observed that not only the infarcted but also the noninfarcted myocardium undergoes significant metabolic alterations following coronary artery ligation.[9] It was, therefore, of interest to examine the fate of norepinephrine in the noninfarcted myocardium following infarction. In the present study the norepinephrine content was determined in infarcted and in noninfarcted tissue of all 4 chambers of the heart following coronary artery occlusion. An attempt was made to relate these observations to changes in left ventricular function and energy metabolism.

Methods

Experiments were performed on 57 mongrel dogs, weighing 14 to 21 kg. The animals were anesthetized with sodium pentobarbital 25 mcg per kilogram. Thoracotomy was performed through the left fifth intercostal space and several branches of the left anterior descending and circumflex coronary arteries were ligated to produce an anterolateral infarction of approximately uniform size, comprising 25 per cent to 30 per cent of the left ventricular muscle mass. On sham-operated animals, the same procedure was carried out except for ligation of the coronary artery branches.

At varying intervals from 1 to 42 days following myocardial infarction the animals were restudied. They were anesthetized with a combination of sublimaze (0 04 mcg per kilogram of body weight) naprine

From Wayne State University, Department of Medicine, Detroit, Mich.
This work was supported by the American Medical Association, Education and Research Foundation, and The Michigan Heart Association.
Received for publication March 6, 1970.
Reprint requests to: Sigmundur Gudbjarnason, Ph.D., Research Associate Professor, Wayne State University School of Medicine, Department of Medicine, 1400 Chrysler Freeway, Detroit, Mich. 48207.
*Research Fellow in Cardiology, Wayne State University, Detroit, Mich.
**Recipient of United States Public Health Service Career Development Award, Number 5-K03-HE 31171.

Glucagon per kilogram) and sodium pento- barbital (8 mcg per kilogram) to avoid depression of the respiratory activity. This type of anesthesia was chosen in order to ensure adequate oxygenation of the myocardial tissue during the final procedure. As evident from lactate and pyruvate determinations no detectable tissue anoxia developed in sham-operated animals or noninfarcted cardiac muscle of experimental animals.

Catheters were placed in the left ventricle and descending aorta and directly connected to P 23 DB Statham strain gauges. Pressures were recorded on an Electronics for Medicine Recorder; the zero level was set at the left ventricular apex. Left ventricular end-diastolic pressure was recorded at the end-expiratory phase of the respiratory cycle using higher sensitivity. The first derivative of the left ventricular pressure pulse (dp/dt) was obtained by means of an R C differentiating circuit.

Upon completion of these measurements the animal was put to death by an intravenous injection of saturated potassium chloride solution. The heart was removed and dissected on crushed ice. Samples were frozen in liquid nitrogen and kept frozen until homogenized.

The endogenous norepinephrine content was determined in both atria, right ventricle, and noninfarcted left ventricle at the base and apex and in the infarcted tissue. The infarcted and noninfarcted areas of the left ventricle were differentiated from each other by means of the changes in color and appearance. The infarcted area appears dull brownish blue in color and shows signs of fatty infiltration or fibrosis on dissection, while the noninfarcted area shows the normal shine and is pink. The definition of noninfarcted muscle was made on the basis of absence of biochemical changes indicative of ischemia or infarction. Those include (1) absence of significant changes in lactate or pyruvate levels or the lactate pyruvate ratio, (2) absence of significant changes in water or hydroxyproline content excluding edema or fibrosis as significant contributing factor, and (3) histologic examination failed to show any signs of infarction in this area of the heart. The determination of norepinephrine was done in 2 gram tissue samples which were grossly freed from blood, fat, and connective tissue, (one gram for atria respectively) according to the method of Anton and Sayre[14] as modified by de Champlain, Krakoff and Axelrod.[15] Recoveries were determined in duplicate with each assay and the results were corrected accordingly. The average recovery was 77.4 ± 7.7 per cent S.D. All determinations for the left ventricular tissue content were done in duplicate. The standard deviation for these duplicates was ± 5.4 per cent. Results were expressed in microgram norepinephrine per gram of wet tissue. Adenosine triphosphate (ATP) and lactate were determined in myocardial biopsy samples taken by means of a bone rongeur precooled in liquid nitrogen as reported previously.[12] ATP was determined according to Adam[17] and lactate was determined according to Hohorst[18] as described previously.[12]

The animals were divided into three major and seven minor groups. Major groups were those depicting the maximal changes in cardiac norepinephrine content, consisting of control (N = 11) and animals put to death 10 days (N = 11) and 6 weeks (N = 9) after infarction. The other groups consist of three animals each and are merely present to illustrate the time course of the change in norepinephrine content. In addition, 5 sham-operated animals were studied 10 days after the initial operation. The surgical procedure was identical and the heart was manipulated in the same manner as before except for the omission of coronary artery ligations. These animals, therefore, reflect the conditions after anesthesia, operational procedures, and re-anesthesia without myocardial infarction.

Results

The infarcted tissue shows a rapid decline in norepinephrine content from the control level of 0.98 ± 0.03 μg NE to 0.35 ± 0.06 μg NE on the first day after infarction. On the second day the infarcted tissue contained 0.06 ± 0.04 μg NE and from the fourth day on, no norepinephrine can be detected in the infarcted tissue (Fig. 1).

In the noninfarcted tissue of the left ventricle a continuous decline in norepinephrine content could be observed during

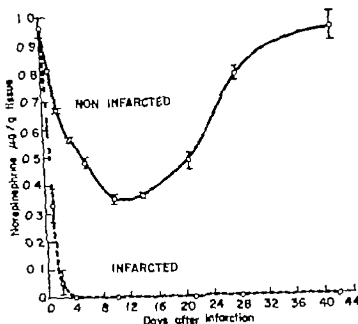


Fig. 1 Changes in tissue content of norepinephrine in infarcted and noninfarcted heart muscle. Vertical lines represent the standard error of the mean

the first ten days following infarction in the apical region as well as at the basilar portion of the ventricle (Figs. 1 and 2) The norepinephrine content at the basilar region fell from 0 98 ± 0 03 µg to 0.35 ± 0 01 µg on the tenth day ($p < 0.001$) and in the apex the norepinephrine content decreased from 0.56 ± 0 02 to 0 14 ± 0 05 µg NE per Gm of tissue during this time ($p < 0.001$) In the right ventricle, the findings were similar norepinephrine levels fell from a control level of 0 93 ± 0 04 to 0.32 ± 0 03 on the tenth day ($p < 0.001$) i.e. both ventricles showed a decline in norepinephrine content to roughly one third of the normal levels during the first ten days following infarction Until the fourteenth day no significant increase toward normal could be observed but during the following four weeks both ventricles showed a gradual continuous rise in NE content, reaching the original values again at the end of the sixth week following myocardial infarction.

Sham-operated animals did not show a decline in myocardial NE content, ten days after operation the values for the left ventricle were 0 96 ± 0.07 µg in contrast to 0.35 ± 0.01 for animals with myocardial infarction. For the right ventricle the values were 0 94 ± 0.05 µg and 0.32 ± 0 03 µg respectively

Both atria showed a similar but less extensive decline in their norepinephrine content (Fig 3) The lowest level in the left atrium was reached after two weeks, decreasing from 1.81 ± 0.13 to 1.21 ± 0 18 µg of NE. The lowest level for the right atrium was reached three weeks after infarction diminishing from 1.88 ± 0.07 to 1.23 ± 0.08 µg NE per Gm. of tissue. Thereafter the NE levels rose gradually and reached the control level by the sixth week following the infarct.

The maximal rate of left ventricular pressure rise fell from a control value of 4 777 ± 265 to 2 676 ± 303 mm Hg per second on the first day following infarction. Subsequently a gradual increase was observed until control levels were reached by the fourth week following myocardial infarction A comparison between left ventricular dp/dt and additional hemodynamic parameters, such as stroke work and stroke volume, which were obtained by means of indicator dilution, showed a close parallelity The stroke work fell from 36 0 ± 3.2 Gm to 11.8 ± 1.5 Gm on the first day

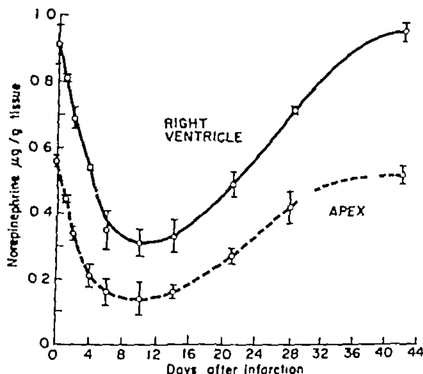


Fig. 2. Tissue content of norepinephrine in right ventricle and apex following myocardial infarction. Vertical lines represent the standard error of the mean.

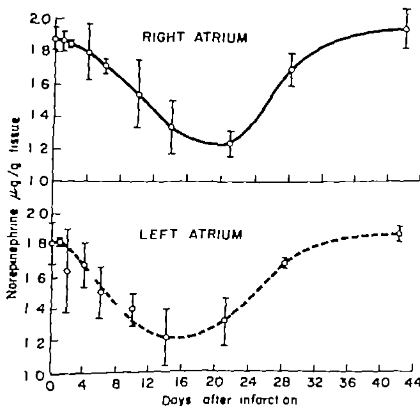


Fig. 3. Changes in atrial tissue content of norepinephrine following myocardial infarction. Vertical lines represent the standard error of the mean.

following infarction. The stroke volume fell from 25 9 ± 1.2 ml. to 13.0 ± 2 0 ml. 24 hr after infarction. Both parameters rose parallel to the increase in dp/dt, and reached control values by the fourth week after infarction.[22] No correlation between peak left ventricular dp/dt and NE content was found. The decrease and subsequent increase in left ventricular (LV) function after infarction was followed by similar changes in NE content (Fig 4)

Table I illustrates an apparent myocardial hypertrophy ensuing after infarction expressed in heart and chamber to body weight ratio The heart weight/body weight ratio increased by 11 6 per cent ($p < 0.05$) and the left ventricle to body-weight ratio increased by 12 7 per cent ($p < 0.05$) The average heart weight of control dogs was 105 4 ± 7 9 grams versus 115 1 ± 7 7 grams 10 days after infarction The body weight of controls averaged 17 0 ± 1 44 versus 16.0 ± 1 1 Kg in dogs ten days after infarction. Since the body weight of experimental animals was somewhat lower than that of the control group a portion of the increase in the heart weight/body-weight ratio may be artifactual due to fall in body weight. The small if any real hypertrophy consequently cannot account for the marked diminution in norepinephrine stores in non infarcted muscle

Fig 5 shows the changes in tissue levels of *ATP* following myocardial infarction[22] in comparison to left ventricular norepinephrine content. The ATP level fell from 5.8 μmole per gram to 2 7 μmole per gram 24 hours after myocardial infarction In creased subsequently and reached a level of 4.6 μmole per gram on the tenth day During this time the norepinephrine content of the tissue showed a continuous decline and reached the lowest level on the tenth day No correlation between these variables was observed. Tissue levels of lactate showed an insignificant increase in noninfarcted muscle during the first two days after infarction thereafter the lactate

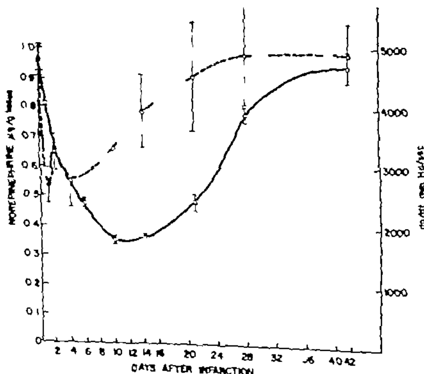


Fig. 4 Comparison between left ventricular function (broken line) and tissue content of norepinephrine (solid line) following myocardial infarction. Vertical lines represent the standard error of the mean.

Table I Compensatory cardiac hypertrophy induced by coronary artery ligation

Variables	TH/BW	LV/BW	RV/BW	S/BW
Control N = 11	6.24 ± 0.16	3.32 ± 0.11	1.55 ± 0.06	1.52 ± 0.06*
10 days after infarct N = 11	6.97 ± 0.29	3.74 ± 0.16	1.76 ± 0.07	1.71 ± 0.09*
% change	+11.6	+12.7	+13.5	+12.5
	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$

Abbreviations: TH = Total heart weight (LV + RV + S) in grams; BW = body weight in kilograms; LV = left ventricular weight in grams; RV = right ventricular weight in grams; and S = septal weight in grams.
*Relative heart weight, grams/kilograms ± SE.

content remained normal (Fig. 6). No correlation between the decline in norepinephrine content and changes in lactate levels in the noninfarcted left ventricular myocardium was observed, excluding the possibility that ischemia of the noninfarcted myocardium might be responsible for the diminution in NE stores.

Discussion

The results of the present study illustrate a marked decline in norepinephrine content of the entire heart following myocardial infarction. Previous studies[1-4] have demonstrated a significant elevation in plasma levels of norepinephrine following myocardial infarction accompanied by increased urinary excretion of this compound, illustrating a marked increase of sympathetic activity following infarction. The significant reduction in norepinephrine content in the entire heart following myocardial infarction could be the result of increased activity of the sympathetic nervous system gradually leading to a marked reduction in cardiac norepinephrine stores. A similar increase in activity of the sympathetic nervous system is present in congestive heart failure and hemorrhagic shock and is known to result in reduction of norepinephrine stores in heart muscle.[23,31-33]

In order to determine whether the observed decline in norepinephrine content was a true decrease or an effect of dilution of the sympathetic nerve endings due to myocardial hypertrophy, the heart/body weight ratio was determined (Table I). Although the ratio for the left ventricle increased significantly, it must be taken into consideration that the infarcted tissue has a higher water content (83.8 per cent ± 0.7 per cent) at this time than noninfarcted muscle (78.5 ± 0.4 per cent),[19] making the increase in total muscle mass appear too large. Even if this is not taken into consideration, the amount of hypertrophy observed could account for only a fraction of the observed decline in norepinephrine content.

Examination of the myocardial water content revealed that no appreciable amount of edema does develop in noninfarcted muscle. Determination of the proline/hydroxyproline ratio in noninfarcted heart muscle showed no change following myocardial infarction, excluding increased fibrosis as a cause for the decrease in norepinephrine content.[19]

As evident from comparison with the lactate content in noninfarcted heart muscle (Fig. 6), the decrease in norepinephrine is unrelated to changes in oxidative metabolism of noninfarcted heart muscle following infarction. Lactate levels showed only minor variations and reached control levels by the fourth day, whereas norepinephrine continued to decline at this time.

It was of special interest to relate the changes in ATP content of the noninfarcted muscle to alterations in norepinephrine levels because this amine is assumed to be stored in sympathetic nerve endings as an ATP norepinephrine complex.[27-31] The greatest decrease in ATP levels was observed 24 hours after infarction (Fig. 5) at a time when norepinephrine levels were not significantly different from control values. The ATP content gradually returned toward normal values, whereas norepinephrine levels continued to decline

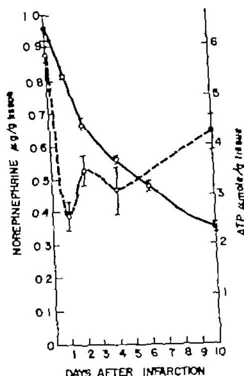


Fig. 5 Comparison between tissue levels of ATP (broken line) and norepinephrine (solid line) in the noninfarcted left ventricular myocardium. Vertical lines represent the standard error of the mean.

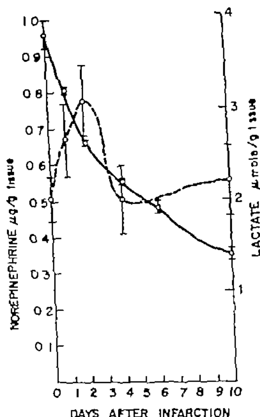


Fig. 6 Comparison between tissue levels of lactate (broken line) and norepinephrine (solid line) in noninfarcted left ventricular myocardium. Vertical lines represent the standard error of the mean.

during the first 10 postinfarction days. It ppears that the decline in norepinephrine is unrelated to alterations in ATP levels of noninfarcted myocardium.

Although several studies suggest that intact norepinephrine stores are necessary to maintain the contractile state of the heart muscle,[20-23] more recent reports indicate that the intrinsic contractile state of the myocardium is not affected by changes in norepinephrine concentration of the heart muscle.[11,24,25] Covell Chidsey and Braunwald[12] found however that the reduction in norepinephrine stores in congestive heart failure, which was more marked than in the present investigation had a direct bearing on the cardiac response to postganglionic sympathetic nerve stimulation in experimental heart failure. The uthors claim that norepinephrine depletion interferes with the ability of the adrenergic system to support the failing myocardium and in this manner many intensify the congestive heart failure state

In our study we found no correlation between tissue levels of norepinephrine and left ventricular function as reflected in the maximal rate of pressure rise. Although a change in the neuronal uptake mechanism or a decline in the de novo synthesis of norepinephrine could account for a similar picture, the observation that both decline and recovery of left ventricular function were closely followed by similar alterations in cardia norepinephrine content suggests that the increased sympathetic activity after infarction might be responsible for the decline in myocardial norepinephrine content. The hypertrophy developing after infarction will compensate for the loss in functional tissue, and while the heart is regaining its normal function the activity

of the sympathetic nervous system returns to normal allowing the tissue stores of norepinephrine to return to their original level

Summary

Serial determinations of the norepinephrine content in all four chambers of the canine heart were carried out following surgical myocardial infarction The observed changes were related to myocardial function and metabolic alterations. Normal left ventricular muscle contained 0 98 μg NE per gram tissue but following coronary artery occlusion the infarcted tissue lost its norepinephrine content completely by the fourth day and the noninfarcted tissue showed a marked decline during the first ten days reaching a level as low as 0 35 μg in the basilar and 0 14 μg NE per gram in the apical portion of the left ventricle The decrease in myocardial norepinephrine content extended to the right ventricle and both atria as well Norepinephrine levels rose again two weeks after infarction and reached normal values six weeks after coronary artery occlusion No correlation was found between norepinephrine content and tissue levels of lactate or ATP in the noninfarcted myocardium Both the decline and recovery of left ventricular function after infarction were followed rather than preceded or accompanied by similar alterations in the norepinephrine content

REFERENCES

1 Richardson J A Woods, E. F and Bagwell E. E. Circulating epinephrine and norepinephrine in coronary occlusion, Amer J Cardiol 5:613 1960.
2. Richardson, J A Circulating levels of catecholamines in acute myocardial infarction and angina pectoris, Progr in Cardiovasc. Dis 6:56, 1963
3 Klein, R. F Troyer W G. Thompson, H K. Bogdonoff M D and Wallace A. G Catecholamine excretion in myocardial infarction Arch. Intern. Med 122:476, 1968
4 Valori C. Thomas, M and Shillingford J P Urinary excretion of free noradrenaline and adrenaline following acute myocardial infarction, Lancet 1:127 1967
5 Chidsey C. A., Harrison D C. and Braunwald E. Augmentation of the plasma norepinephrine response to exercise in patient with congestive heart failure New Eng J Med 267:650, 1962.
6. Lammerant, J Dellert, P., and DeSchryver C. Direct release of catecholamines into the left heart chambers. The enhancing effect of acute coronary occlusion, Arch. Intern. Pharmacol 163:219 1966.
7 Wollenberger A., Krause E. G., and Shahab, L. Endogenous catecholamine mobilization and the shift to anaerobic energy production in the acutely ischemic myocardium, in Marchetti, G and Taccardi B editors. Coronary circulation and energetics of the myocardium, Basel and New York 1967 S. Karger AG, p. 200.
8 Russell R. A., Crafoord, J and Harris A S. Changes in myocardial composition after coronary artery ligation Amer J Physiol. 200:995, 1961
9 Gudbjarnason, S Braasch W Cowan, C., and Bing R. J Metabolism of infarcted heart muscle during tissue repair Amer J Cardiol 22:360 1968.
10 Gudbjarnason S., Braasch W and Bing, R. J Defective energy metabolism and fatty degeneration in heart muscle in Reindell, H., Keul, J and Doll, E., editors Heart failure pathophysiological and clinical aspects, Stuttgart, 1968 Georg Thieme Verlag p. 233.
11 Gudbjarnason S., Braasch W and Bing R. J Protein synthesis in cardiac hypertrophy and heart failure, in Reindell H. Keul, J and Doll, E. editors. Heart failure Pathophysiological and clinical aspects, Stuttgart, 1968, Georg Thieme Verlag p. 185.
12 Braasch W Gudbjarnason, S Puri, P S Ravens, K. C. and Bing R. J Early changes in energy metabolism in the myocardium following acute coronary artery occlusion in anesthetized dogs, Circ. Res. 23:429 1968.
13 Puri, P S. and Gudbjarnason, S. Myocardial high energy phosphate level and left ventricular function following coronary artery occlusion in anesthetized dogs (In preparation.)
14 Anton, A. H and Sayre, D F A study of the factors affecting the aluminum oxide-trihydroxyindole procedure for the analysis of catecholamines, J Pharmacol. Exp. Ther 138:360, 1962
15 de Champlain, J Krakoff L. R. and Axelrod J Catecholamine metabolism in experimental hypertension in the rat Circ Res. 20:136, 1967
16. V Euler U S and Lishajko, F Improved technique for the fluorometric estimation of catecholamines, Acta Physiol. Scand. 51:348 1961
17 Adam H Adenosin 5 triphosphate determination with phosphoglycerate kinase in Bergmeyer H U editor Methods of enzymatic analysis, New York, 1963 Academic Press Inc p. 539
18. Hohorst H J L − (+) − Lactate Determination with lactic dehydrogenase and DPN in Bergmeyer H U editor Methods of enzymatic analysis, New York, 1963 Academic Press Inc p. 266
19 Gudbjarnason S. Changes in proline and hydroxyproline content in infarcted and noninfarcted heart muscle. (In preparation.)
20. Chidsey C. A Braunwald E., and Morrow

R. G. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure Amer J Med. 39:442, 1965.

21 Spann, J F Sonnenblick, E. H., Cooper T Chidsey C A., Willman, L. V and Braunwald, E. Cardiac norepinephrine stores and the contractile state of heart muscle, Circ. Res. 19:317 1966.

22. Covell, J W Chidsey C. A., and Braunwald, E. Reduction in the cardiac response to postganglionic sympathetic nerve stimulation in experimental heart failure, Circ. Res. 19:51 1966.

23. Chidsey C. A., Kaiser G. H., Sonnenblick, E. H Spann, J F and Braunwald, E.. Cardiac norepinephrine stores in experimental heart failure in the dog J Clin. Invest. 43:2386, 1964.

24. Tomomatsu, T Ueba, Y Matsumoto, T Ikoma, T and Kondo, Y Catecholamine in congestive heart failure Jap. Heart J 4 13 1963

25 Coleman, B., and Glaviano, V. V.. Tissue levels of norepinephrine and epinephrine in hemorrhagic shock, Science 139:54, 1962.

26. Hift H and Campos, H. A.. Changes in subcellular distribution of cardiac catecholamines in dogs dying from irreversible hemorrhagic shock, Nature (London) 196:678, 1962.

27 Iversen L. L.. Storage of noradrenaline in intracellular particles in adrenergic nerves, in The uptake and storage of noradrenaline London, 1967 Cambridge University Press, p. 41

28. Weiner N and Jardetzky O A study of catecholamine nucleotide complexes by nuclear magnetic resonance spectroscopy Arch. Exp. P th. Pharmacol. 248:308 1964

29 Wurtman, R. J Catecholamines, New Eng. J Med. 273:637 1965

30. Potter L. T., and Axelrod, J Property of norepinephrine storage particles of rat heart, J Pharmacol. Exp. Ther 142:299 1963.

31 Von Euler U S., Lishajko, F and Stjarne, L. Catecholamines and adenosine triphosphate in isolated adrenergic nerve granules, Acta Physiol. Scand. 59:495, 1963.

32. Lee, W C., and Shideman, F E.: Role of myocardial catecholamines i cardiac contractility Science 129:967 1959

33. Whalen, W J Fishman, N and Erickson, R.. Nature of the potentiating substance in cardiac muscle Amer J Physiol 194:573 1958.

34. Maxwell, R. A., Kelley J J and Eckhardt E. T Effect of catecholamine depletion on n index of cardiac contractility in isolated rabbit hearts, Proc. Soc. Exp. Biol. Med. 116:672 1964

35. Koch-Weser J Role of norepinephrine release in the interval strength relationship of heart muscle, J Pharmacol Exp. Ther 150 184 1965

Action of pharmacologic agents in experimental cardiac tamponade

Robert E. Finegan, M.D.
Marianne Schroll
Sherilyn Robison
Donald C. Harrison, M.D.
Palo Alto, Calif.

Previous work from this laboratory has shown that isoproterenol given by bolus injection was effective in reversing the hemodynamic abnormalities of acute experimental pericardial tamponade.[1] Isoproterenol produced a fall in right atrial pressure, an increase in heart rate, an increase in stroke volume, and a marked increase in cardiac output. Systemic vascular resistance fell in response to isoproterenol. Acute volume loading to a lesser extent also increased cardiac output, but right atrial pressure increased. In contrast, acetylstrophanthidin did not increase stroke volume or cardiac output. It was postulated that this occurred because acetylstrophanthidin also increased systemic vascular resistance, and thus the positive inotropic effects of this drug were counterbalanced by an increase in afterload.

The present study was designed to assess independently the relative importance of each of these physiologic parameters in acute experimental tamponade. Atrial pacing was studied in an attempt to assess the effects of increased heart rate alone. An infusion of isoproterenol was substituted for the bolus injection technique to more closely simulate clinical situations, and during the isoproterenol infusion right atrial pressure was maintained by infusion of added volume into the pericardial space, in order to control for the reduction in right atrial pressure produced by isoproterenol. Methoxamine, an alpha-adrenergic stimulator with no known positive inotropic effects,[2] was given in order to study the effect of an isolated increase in systemic vascular resistance. Ouabain was given instead of acetylstrophanthidin since the latter agent is not available for use in man, and atrial pacing was repeated during the period of ouabain administration in order to duplicate the rate increase produced by isoproterenol.

Methods

Mongrel dogs weighing between 11 and 18 Kg. (mean 14 Kg.) were anesthetized with intravenous pentobarbital and ventilated with a Harvard Pump while a catheter was inserted in the pericardial space

From the Cardiology Division, Stanford University School of Medicine, Palo Alto, Calif.

This work was supported in part by National Institutes of Health Grants HE-09058, HE 5709, and HE-03866, and grant from the National Aeronautic and Space Administration, No. NGL-05-020-305.
Received for publication March 21, 1970.

Reprint requests to: Dr. Donald C. Harrison, Chief, Cardiology Division, Stanford University School of Medicine, Palo Alto, Calif. 94305.

through a water tight seal utilizing a right lateral thoracotomy A polyethylene catheter and a pacing catheter were placed in the right atrium by a transvenous route and their position was confirmed by palpation The chest was closed and the pneumothorax was evacuated Catheters were also placed in the descending aorta for pressure measurement in a femoral artery for blood withdrawal and in a femoral vein for drug infusion Pressures were measured with Statham p23Db transducers and a Honeywell recorder Serial cardiac outputs were performed in duplicate with the dye-dilution technique.

Tamponade was created by infusing saline into the pericardial space in order to raise the right atrial and pericardial pressures from 7 to 10 mm. Hg Any animal demonstrating a leak or a rapid decline in intrapericardial pressure was discarded. It was necessary to add small amounts of saline to the pericardial space to re-establish the original level of tamponade in a few dogs.

Isoproterenol was given as an infusion of 5 μg per minute As in the previous study isoproterenol caused a fall in right atrial pressures and following stabilization of pulse rate and aortic pressure the level of tamponade was increased by volume infusion into the pericardial space to restore the right atrial and pericardial pressures to those present before beginning isoproterenol and the infusion was continued The animal was allowed to stabilize, and measurement of outputs and pressures were made.

Ouabain was given as a single dose of 25 μg per kilogram Methoxamine was infused in doses of 0 1 to 0 6 μg per kilogram per minute The position of the pacing electrode was manipulated to achieve effective pacing if necessary After each period of pacing or drug infusion the animal was allowed to return to the previous heart rate and control measurements were again made in duplicate as controls for the next condition change At least one hour elapsed after the infusion of ouabain before measurements were made. All measurements were made during spontaneous respiration. A light plane of anesthesia was maintained by additional small doses of pentobarbital. Complete experiments were made in 14 animals. Only 5 were treated with methoxamine but 14 received isoproterenol and ouabain and were paced before and after digitalization at the same rate as occurred during the administration of isoproterenol. The order in which studies were made was varied randomly except for the administration of ouabain which was given last in all experiments When pacing preceded isoproterenol the animal was paced at two rates to 'bracket' the rate anticipated during isoproterenol infusion

Results

The circulatory effects of acute pericardial tamponade are shown in Table I There was a significant rise in right atrial pressure heart rate and systemic vascular resistance and there was a significant fall in stroke volume cardiac output, and aortic pressures.

Isoproterenol infusion reversed many of the effects of tamponade (Table II) Heart rate, cardiac output, and stroke volume rose significantly with a concomitant fall in systemic vascular resistance. The mean aortic pressure was unchanged Atrial pacing at a rate similar to that attained

Table I Hemodynamic effects of pericardial tamponade

Parameters	Control	Tamponade	Significance
Heart rate	167 ± 19	181 ± 26	< 0 001
Right atrial pressure (mm. Hg)	0 2 ± 3	7 ± 1	< 0 001
Mean aortic pressure (mm Hg)	141 ± 5	122 ± 5	< 0 003
Cardiac output (L./min)	3 3 ± 0 2	1 4 ± 0 3	< 0 001
Stroke volume (c c.)	20 ± 1	8 ± 1	< 0 001
Systemic vascular resistance (mm. Hg/L /min)	48 ± 15	87 ± 26	< 0 001

Table II Effects of isoproterenol in pericardial tamponade

Parameters	Before isoproterenol	After isoproterenol	Significance
Heart rate	180 ± 26	212 ± 27	< 0 001
Mean aortic pressure (mm Hg)	1 5 ± 7	122 ± 5	N.S.
Cardiac output (L/min)	1 5 ± 0 1	2 8 ± 0	< 0 001
Stroke volume (c c)	8 3 ± 0 8	13 3 ± 1 0	< 0 001
Systemic vascular resistance (mm Hg/L /min)	87 ± 26	49 ± 21	< 0 001

N S = Not significant

Table III Effects of atrial pacing in pericardial tamponade

Parameters	Pre pace	Pacing	Significance
Heart rate	187 ± 25	217 ± 26	< 0 001
Mean aortic pressure (mm Hg)	130 ± 4	1 5 ± 3	N.S.
Cardiac output (L /min)	1 5 ± 0 1	1 5 ± 0 1	N.S.
Stroke volume (c.c)	7 7 ± 2 4	7 ± 2 3	N.S.

during isoproterenol infusion failed to alter any of the measured parameters (Table III)

Ouabain administration (Table IV) resulted in a small but significant fall in cardiac output and stroke volume and a rise in systemic vascular resistance The mean aortic pressure and heart rate were unaffected by ouabain Atrial pacing after ouabain resulted in a small fall in stroke volume but had no other effect

The administration of methoxamine produced a decrease in heart rate and a marked rise in systemic vascular resistance Concomitantly there was a significant fall in stroke volume and cardiac output (Table V) The effects of the pharmacologic agents are summarized in Figs. 1 through 5

Discussion

The degree of circulatory embarrassment produced by pericardial tamponade in these studies is characterized by the marked fall in cardiac output and arterial pressure associated with a rise in right atrial pressure and systemic vascular resistance This well known[3] hemodynamic pattern of restricted cardiac filling was almost completely reversed by the infusion of isoproterenol There was an increase in both heart rates and a more marked increase in stroke volume These changes are in agreement with the earlier observation reported from this laboratory when bolus injections of isoproterenol were given in acute pericardial tamponade[1]

In order to maintain the filling pressure on the right side of the heart as near as possible to control levels the level of tamponade was increased while isoproterenol administration was continued in order to raise right atrial and intrapericardial pressures to levels that had been observed prior to beginning the infusion In spite of this maneuver the cardiac output heart rate and stroke volume were maintained at levels similar to those observed during the control period prior to the production of pericardial tamponade

In an attempt to determine whether or not the circulatory changes produced by isoproterenol were due to an increase in heart rate alone atrial pacing was performed at a rate similar to the rate induced by isoproterenol Pacing alone did not reverse any of the hemodynamic abnormali

Table IV Effects of ouabain and atrial pacing in pericardial tamponade

Parameters	Pre-ouabain	Ouabain	Significance	Ouabain and pace	Significance
Heart rate	164 ± 34	173 ± 30	N.S.	214 ± 27	< 0.001
Mean aortic pressure (mm. Hg)	131 ± 6	127 ± 7	N.S.	122 ± 3	N.S.
Cardiac output (L./min.)	1.5 ± 0.1	1.2 ± 0.1	< 0.01	1.3 ± 0.1	N.S.
Stroke volume (c.c.)	9.6 ± 0.8	7.3 ± 0.7	< 0.01	6.3 ± 0.4	< 0.05
Systemic vascular resistance (mm. Hg/L./min.)	87 ± 26	107 ± 30	< 0.01	—	—

Table V Effect of methoxamine in pericardial tamponade

Parameters	Control	Methoxamine	Significance
Mean aortic pressure (mm. Hg)	132 ± 2	144 ± 12	N.S.
Heart rate	185 ± 29	153 ± 19	< 0.05
Cardiac output (L./min.)	1.6 ± 0.6	0.6 ± 0.4	< 0.05
Stroke volume (c.c.)	9 ± 4	4 ± 3	< 0.05
Systemic vascular resistance (mm. Hg)	81 ± 30	285 ± 110	< 0.01

ties produced by tamponade. In addition to pacing as a solitary maneuver atrial pacing following the administration of ouabain produced no significant circulatory changes even when the heart rates were increased to levels comparable to peak heart rates observed during isoproterenol infusion.

Isoproterenol has been shown to have positive inotropic effects in many studies.[4-6] It has also been shown to result in greater shortening of myocardial segments at end systole when external dimensions of the heart were marked with metal markers and their movements recorded with cine fluoroscopic techniques. The findings in this and in previous studies of pericardial tamponade appear to result from the positive inotropic effects of isoproterenol. This positive inotropic effect occurred during a time when aortic mean pressure (afterload) was unchanged and right atrial filling pressure was elevated to control the ventricular filling pressure. In spite of this maneuver there continued to be a marked increase in cardiac output and stroke volume. This was not due to the increase in heart rate since pacing to comparable heart rates to those observed during isoproterenol did not produce any significant circulatory changes.

The response to ouabain was of interest since a small fall in cardiac output and stroke volume occurred at a time when there was an increase in systemic vascular resistance and arterial pressure. In our previous study the administration of acetylstrophanthidin resulted in slight increases in cardiac output and stroke volume which were not highly significant. It appears that any positive inotropic effects of digitalis glycosides under the altered circulatory conditions produced by pericardial tamponade are counterbalanced by an increase in systemic vascular resistance. This increased resistance has been attributed to a peripheral vasoconstrictor effect of digitalis preparations.[7] It is clear that the circulatory effects of ouabain are not beneficial and are not comparable to those observed during the administration of isoproterenol under these experimental conditions.

In an attempt to assess the effects of the increase in arterial pressure and peripheral resistance alone methoxamine infusions

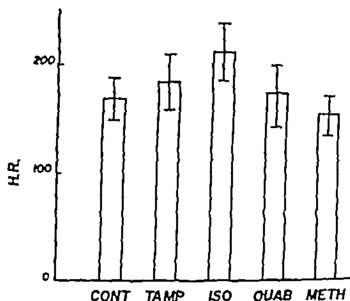


Fig. 1. Heart rate (HR) during control period (CONT), tamponade (TAMP) and in response to drugs. ISO = isoproterenol, OUAB = ouabain, and METH = methoxamine. The bars represent means ± standard error of the means.

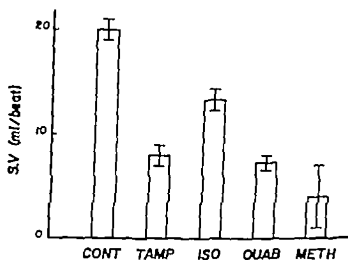


Fig. 2. Effect of tamponade and drugs on stroke volume (SV). Other abbreviations as in Fig. 1.

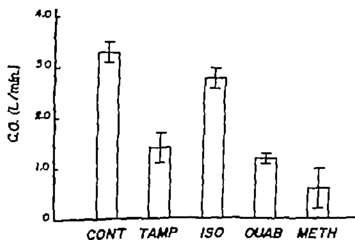


Fig. 3. Effects of tamponade and drugs on cardiac output (CO).

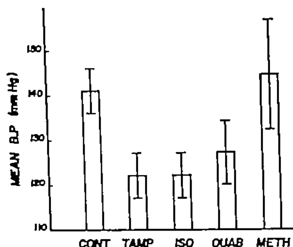


Fig. 4 Effects of tamponade and drugs on mean arterial blood pressure (*MEAN BP*)

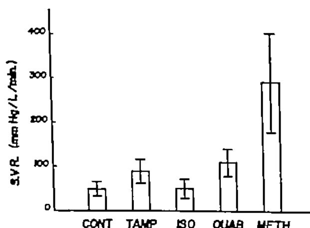


Fig 5 Effects of tamponade and drugs on systemic valvular resistance (*SVR*)

were given to elevate the mean arterial pressure significantly Although methoxamine has been shown to have small beta adrenergic blocking properties in the heart,[8] its primary effect is to elevate arterial pressure by direct stimulation of peripheral alpha adrenergic receptors. During acute tamponade, methoxamine produced a significant rise in systemic vascular resistance and a marked fall in cardiac output and stroke volume. A small but significant fall in heart rate also occurred during infusions of methoxamine. Thus, it would appear that when the filling pressures of the ventricles are impaired by pericardial tamponade, elevations of peripheral vascular resistance are not well tolerated. These findings with methoxamine are similar to those observed with ouabain, but since methoxamine has no positive inotropic effect, the net result is further deterioration of the circulation.

Isoproterenol infusion is clearly effective in improving the altered hemodynamics of experimental pericardial tamponade. It has both positive inotropic and chronotropic effects. Its beneficial circulatory effects appear to be due to a marked positive inotropic effect and only slightly if at all, to its chronotropic effects. Ouabain produces an increase in systemic vascular resistance which counterbalances any positive inotropic effects the drug may have

and its circulatory effects in acute pericardial tamponade are deleterious. The administration of methoxamine produces further deterioration of the circulation in the presence of experimental pericardial tamponade. An understanding of these physiologic principles merits consideration when drugs are used for the treatment of pericardial tamponade in patients prior to the removal of fluid by needle aspiration or pericardiectomy.

Summary

Cardiac tamponade was produced in 14 dogs by infusing saline into the pericardial space. The effect of isoproterenol, atrial pacing, ouabain, and methoxamine were studied after the animals resumed spontaneous respiration. Tamponade significantly reduced arterial pressure, stroke volume, and cardiac output, and significant increases in right atrial pressure, heart rate, and systemic vascular resistance were observed. The administration of isoproterenol resulted in an increase in stroke volume, heart rate, and cardiac output and reduced systemic vascular resistance even when right atrial pressure was maintained by further volume infusion. Atrial pacing did not alter any of the abnormalities observed during tamponade. Digitalization with ouabain was also ineffective in reversing the hemodynamic changes produced by tamponade. The ineffectiveness of digitalization in cardiac tamponade was probably due to an increase in systemic vascular resistance that counterbalanced positive inotropic effects. Methoxamine, by markedly increasing systemic vascular resistance, significantly worsened the hemodynamics of tamponade. It appears that an ideal pharmacologic agent for reversing the hemodynamic alterations of acute cardiac tamponade should have positive inotropic effects to reduce end systolic volume and maximize the ejection fraction and an ideal agent should also increase heart rate and reduce systemic vascular resistance. Isoproterenol combines all of these properties.

REFERENCES

1. Treister, B., Gianelly, R. E., Cohn, K. E., and Harrison, D. C.: The circulatory effects of isoproterenol, acetylstrophanthidin and volume loading in acute pericardial tamponade, Cardiovasc. Res 3:299, 1969.
2. Goldberg, L. I., Bloodwell, R. D., Braunwald, E., and Morrow, A. G.: The direct effects of norepinephrine, epinephrine and methoxamine on myocardial contractile force in man, Circulation 22:1125, 1960.
3. Metcalf, J., Woodbury, J. W., Richards, V., and Burwell, C. S.: Studies in experimental pericardial tamponade. Effects on intravascular pressures and cardiac output, Circulation 5:518, 1952.
4. Fowler, N. O., and Holmes, J. C.: Hemodynamic effects of isoproterenol and norepinephrine in acute cardiac tamponade, J Clin. Invest. 48:502, 1969.
5. Harrison, D. C., Glick, G., Goldblatt, A., and Braunwald, E.: Studies on cardiac dimensions in intact unanesthetized man. IV. Effects of isoproterenol and methoxamine, Circulation 29:186, 1964.
6. Krasnow, N., Rolett, E. L., Yurchak, P. M., Hood, W. B., and Gorlin, R.: Isoproterenol and cardiovascular performance, Amer. J. Med. 3:514, 1964.
7. Ross, J., Waldhausen, J. A., and Braunwald, E.: Studies on digitalis. I. Direct effects on peripheral vascular resistance, J. Clin. Invest. 39:930, 1960.
8. Blinks, J. R.: The nature of the antagonism by methoxamine of the chronotropic and inotropic effects of catecholamines, Arch. Exp. Path. Pharm. 218:73, 1964.

The differential effects of ouabain on sinus A-V nodal, His bundle, and idioventricular rhythms*

Benjamin J. Scherlag, Ph.D.
José L. Abelleira, B.S.
Onkar S. Narula, M.D.
Philip Samet, M.D.
Miami Beach, Fla.

Recently a systematic investigation of the action of ouabain on cardiac rhythmicity demonstrated a biphasic chronotropic effect of this glycoside on the sinus node. After the initial slowing there was a later increase in the rate of this pacemaker. These same authors also reported a similar biphasic rate response to ouabain in dogs with complete heart block and idioventricular rhythms.

The effect of digitalis on rhythms arising in the proximal A-V junction (A-V node and His bundle) has resulted in an increase[4] or a decrease[5] in the rate of these pacemakers. Recently the exact localization of A-V junctional rhythms has been a subject of discussion.[7]

The present study was designed to determine the effects of ouabain on experimentally induced A-V junctional rhythms as well as to re-examine this glycoside's effects on sinus and idioventricular rhythms in anesthetized dogs. In the course of these pharmacodynamic studies, evidence has been obtained which has bearing on the locus of pacemaker activity in the A-V junction.

Methods

Twenty-three adult mongrel dogs anesthetized with Nembutal, 30 mg. per kilogram administered intravenously, were used in this study. Six animals were studied during sinus rhythm continuously monitored by a standard Lead II electrocardiogram. Ouabain in a dose of 10 μg per kilogram was administered intravenously every 10 minutes until toxicity, manifested as ventricular tachycardia, occurred. One to two weeks later these six were studied again. Also 17 others not previously studied were anesthetized and, under controlled ventilation, a thoracotomy was performed through the right fourth intercostal space. The pericardium was incised and the right atrium and base of the right ventricle exposed. Two Teflon-coated stainless steel wires were then inserted into the region of

From the Division of Cardiovascular Disease, Department of Internal Medicine, Mount Sinai Hospital, Miami Beach, Fla.

This work was carried out under grant-in-aid of the Florida Heart Association and supported by the Heart Association of Broward County and the Heart Association of Palm Beach County No. 69 AG 11.
Received for publication March 23, 1970.

Reprint requests to: Dr. B. J. Scherlag, Division of Cardiology, Department of Internal Medicine, Mt. Sinai Hospital, 4300 Alton Road, Miami Beach, Fla. 33140.

A preliminary report of this work was presented at the Federation of American Societies for Experimental Biology, Atlantic City, April, 1969.

Table I Initial heart rates during sinus A V nodal His bundle and idioventricular rhythms

Experiment number	S-A HR	A V HR	HB HR	IVR HR
1	200	100	53	47
2	171	96	50	46
3	160	95	47	45
4	141	92	41	45
5	125	76	35	44
6	124	135	32	36
7	170	123	30	31
8	16	7[illegible]	28	43
9	120	72	38	—
10	150	75	—	—
Mean HR	152	91	39	4
S D	±25	±22	±9 0	5 2
Significance		$p < 0.001$ (A V vs HB)		
			$p > 0.4$ (HB vs IVR)	

Abbreviations HB = His bundle IVR = idioventricular rhythm; and HR = heart ra

the His bundle through the lateral atrial wall and connected through a switch box to an A C amplifier in order to record a bipolar His bundle electrogram [9] In several of the experiments His bundle activity was recorded from a bipolar electrode catheter inserted through a femoral vein and stabilized in the region of the A V junction [9,10]

Induction of A V nodal His bundle and idioventricular rhythms In one group of animals, A V nodal escape rhythms were induced by constant cooling of the S-A nodal region using a silver cooling coil [11] In the other dogs the S-A node was crushed thus inducing an A V junctional rhythm These rhythms quickly stabilized displayed a slow heart rate (Table I) and in most instances the entire P wave was temporally simultaneous with the QRS complex (mid nodal rhythm) In every case the His bundle deflection preceded atrial activation (Fig 1) Since atrial activity recorded in the His bundle electrogram emanates from atrial tissue directly adjacent to the A V node[12,13] the reversal of atrial and His bundle deflections is compatible with an A V junctional rhythm The relevance of the term A V junctional rhythm will be discussed below His bundle rhythms, subsequent to complete heart block, were produced by the localized injection of 0 3 to 0 5 c.c of formaldehyde into the A V nodal region through the lateral atrial wall [4] Complete heart block followed by idioventricular rhythms was induced by injecting the His bundle and A V nodal regions with 0.3 to 0.5 c.c of formaldehyde in a similar manner as above. Two dogs with complete heart block and His bundle rhythms and three dogs with idioventricular rhythms were also studied on a chronic basis

After stable control records were obtained during a given rhythm i.e. A V nodal His bundle or idioventricular ouabain 10 μg per kilogram was injected intravenously every 10 minutes. Lead II and central aortic blood pressure were monitored continuously All recordings were made on an Electronics for Medicine oscillographic photographic recorder at paper speeds of 25 and 100 mm per second with 1 second time lines

Results

Fig 1 demonstrates in the same animal, the comparative appearance of sinus, A V nodal and His bundle rhythm in a standard Lead II electrocardiogram and a simultaneously recorded bipolar electrogram from the His bundle region During sinus rhythm (130/min) the His bundle electrogram showed atrial activity (A wave) followed by a His bundle deflection (BH) occurring during the isoelectric portion of the P R interval in Lead II and an S wave associated with late depolarization of the base of the ventricular septum During cooling of the S-A node (Fig 1 *B*) the A wave follows the His bundle deflection and falls within the period of ventricular activity A typical A V nodal rhythm at a heart rate of 79/min is seen in the standard electrocardiogram (L-2) In the lower panel (Fig 1 *C*) after complete heart block has been induced by the localized injection of formaldehyde into the A V nodal region His bundle activity still precedes each normal ventricular activation whereas atrial activity is dissociated The ventricular rate has now decreased to 49/min

Table I summarizes the average initial

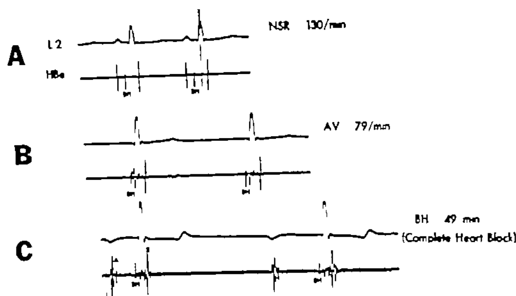


Fig. 1. *A*, *B*, and *C*. Examples of sinus (*NSR*), A-V escape (*AV*) and His bundle rhythms (*BH*). The top trace in each panel is standard Lead II electrocardiogram (*L-2*); below is the His bundle electrogram (*HBe*) showing atrial, A, His bundle, BH, and late activity in the base of the ventricular septum, S wave. *A*, Sinus rhythm at rate of 130/min. with His bundle activity occurring during P-R interval of the surface electrocardiogram. *B*, A-V nodal rhythm at rate of 79/min. produced by cooling the S-A node. Note that His bundle activity precedes atrial activity which in turn occurs prior to ventricular activity. *C*, His bundle rhythm at 49/min. with complete heart block. Note dissociation of atrial activity; however, His bundle deflection precedes each ventricular complex and normal QRS configuration persists. The interval between time lines equals 1 second.

(control) heart rates observed in 10 dogs during normal sinus, 152 ± 24 (S.D.); A-V nodal 94 ± 22; His bundle, 39 ± 9.0; and idioventricular rhythm 42 ± 5.0 beats/min. During digitalization the heart rates generally followed consistent patterns (depending on the character of the initial pacemaker) which persisted until digitalis toxicity supervened. Fig. 2 is a graphic representation of the effects of progressive digitalization on the sinus rate during sinus rhythm; however, just prior to ouabain toxicity the heart rate rose. Fig. 3 shows the effect of ouabain on the average heart rate in those animals with A-V nodal rhythms (7 cases) and idioventricular rhythms (7 cases). The circles represent the mean values of heart rate at each dose level of ouabain; one standard deviation is shown by the vertical bars. During A-V nodal escape rhythms and idioventricular rhythms, ouabain administration resulted in a decrease in the rate of each of these pacemakers until the onset of toxicity. The effect of ouabain on the heart rate during His bundle rhythms with complete heart block is seen in Fig. 4 in each of six animals. With increasing doses of ouabain, there was a tendency for the heart rate to decrease and, except in one case, to increase prior to toxicity. However, the difference in the initial and final heart rate prior to toxicity was small.

The electrophysiological effect of ouabain at toxic levels. During sinus and A-V nodal escape rhythms, ouabain intoxication was manifested as a stable ventricular tachycardia (150 to 180/min.) whose abrupt onset was usually preceded by isolated or several successive ventricular premature contractions. During His bundle and idioventricular rhythms, the onset of ouabain induced ventricular beats was also abrupt and developed in two distinct phases. The initial phase showed a different ventricular focus at either the same or a slightly higher heart rate than the control rhythm and a second phase at a faster rate. Between the two phases, this "toxicity" pacemaker usually disappeared for 1 to 3 minutes and

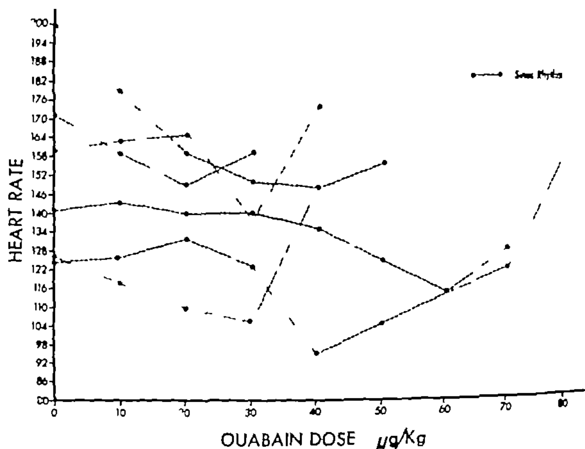


Fig 2 The chronotr pic effect of progressive digitalization in dogs d ring sinus rhyth i. The dose of ouabain in μg per kilogram is shown on the abscissa and sinus rate (beats/min) on the ordinate. In each of 6 dogs progressive d gitalization produced general decrease in sinus rate and in each case a nadir is reached, then there is an increase in rate u til the onset of toxicity Note the wide v riation in the dose at which each animal develops ouabain toxicity (vent cula tachycardia)

reappeared abruptly at a faster rate (average 70 beats/min) then quickly accelerated to 150 to 200 beats/min within 2 to 5 minutes. A typical example of the onset of toxicity during idioventricular rhythm is indicated in Fig 5 The control rhythm shows an idioventricular focus at a rate of 44/min (*A*) With progressive doses of ouabain up to 70 μg per kilogram (70 minutes) there is a decrease in the rate of the control idioventricular pacemaker to 25/min (Fig 5 *B*) Abruptly a new pacemaker manifests itself at 72 minutes which is slightly faster than the previous focus (Fig 5 *C*) and within 2 minutes the ouabain induced ventricular focus was beating at a rate of 69 per minute (Fig 5 *D*)

Discussion

The data obtained in the present study indicate that ouabain exerts qualitatively and quantitatively different effects on various sites of cardiac rhythmicity Previous reports have indicated that cardiac glycosides can depress, enhance or alter A V junctional rhythms. The divergence of these findings with those presented in our study may in part be due to the differences in the preparations utilized and the experimental conditions under which the studies were performed Specifically several investigators working with isolated tissues found no effect of digitalis on the automaticity of A V nodal cells at therapeutic dose levels whereas, at toxic dose levels the automaticity of these cells was enhanced The apparent disagreement of such results may be due to the fact that the in vitro preparation lacks central autonomic innervation thus mitigating the vagal effect of therapeutic levels of digitalis Our data do not correspond with the clinically observed effect of digitalis-induced nodal tachycardia Species

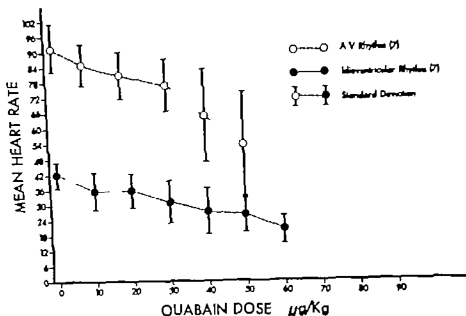


Fig. 3. The chronotropic actions of ouabain on A-V nodal and idioventricular rhythms. Abscissa: Ouabain dose (μg per kilogram). Ordinate: Mean heart rate (beats/min.). Open circles represent mean values in 7 animals with A-V nodal rhythm. Closed circles represent mean values in 7 animals with idioventricular rhythms during complete heart block. The vertical bars show the standard deviation of each mean. As ouabain dose increases, there is consistent decrease in the rate of both A-V nodal and idioventricular rhythms until the onset of digitalis toxicity occurs.

differences notwithstanding, it would seem unlikely that digitalis enhances a His bundle or A-V nodal pacemaker in such cases, although the glycosides may act to potentiate the automaticity of damaged tissue in the A-V node–His bundle region. An other possibility is that these digitalis-induced A-V nodal tachycardias are actually arising in the atrium close to the A-V node or in the left atrium and cannot be differentiated electrocardiographically.

The exact locus of so-called A-V nodal rhythms has recently been the cause of some controversial discussion.[4] On the basis of microelectrode studies, Hoffman[4] has suggested that spontaneous activity was absent in the N regions of the A-V node but does occur in the His bundle or junctional nodal-His bundle (N-H) cells. Watanabe and Dreifus also found no evidence of automatic activity in the cells of the N region of the A-V node. These workers confirmed the findings of N-H cell automaticity and also, in a few cases found slow diastolic depolarization in atrio-nodal (A-N) cells of the A-V node. The result of this controversy has led many investigators to refer to pacemakers residing in the A-V node area as "A-V junctional" pacemakers. However, some pertinent evidence from this and other studies would indicate that a more specific localization of pacemaker origin, i.e., A-V node or His bundle, is possible. Previous microelectrode studies[19] have demonstrated that the components of the A-V node, A-N, N and N-H cells, show relatively similar responses to acetylcholine as compared to the His bundle which is indifferent to concentrations that cause profound effects on both nodes (S-A and A-V) and on the atrium.[19] Another physiological and pharmacological differentiation of A-V nodal and His bundle rhythms has been recently demonstrated in our clinical laboratory. During cardiac catheterization His bundle recordings were obtained in patients with complete heart block and a narrow QRS complex.[20] Those patients with block proximal to the bifurcation of the bundle branches had heart

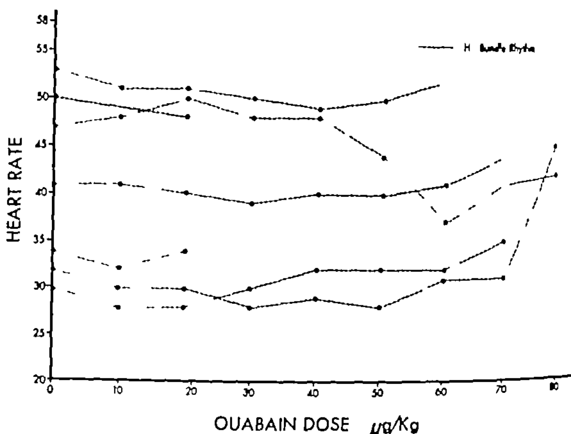


Fig 4 The effect of ouabain on the rate of His bundle pacemakers during complete heart block. Abscissa Ouabain dose (μg per kilogram) Ordinate heart rate (beat /min) The data are plotted separately for each animal and indicate no general trend in His bundle pacemaker rate in response to digitalization. The range of variation of heart rate in each curve and the difference between the initial and final heart rate prior to ouabain toxicity is very small.

rates falling into two groups The range of rates of the upper (A V nodal) rhythms was 48 to 51 beats/min whereas the range of rates of the His bundle rhythms was 30 to 36 beats/min The former group showed a marked increase in ventricular rate after atropine administration (30 to 40 beats/min) However the latter group showed no significant change in heart rate after similar doses of atropine [19, 22] Another study from our laboratory in the intact dog heart has provided further physiological evidence for the differentiation of A V nodal rhythms from induced His bundle rhythms. It was found that retrograde conduction time from the His bundle to sinus node activation was significantly longer during His bundle rhythms (His bundle pacing) than during spontaneous mid or lower nodal rhythms at the same heart rate [23] All these data are consonant with the findings in the present study For example A V nodal escape rates averaged 92 ± 22 beats/min which was significantly different ($p <$ 0 001) than His bundle rhythms whose average rate was 39 ± 9 beats/min In addition progressive doses of ouabain consistently slowed A V nodal rhythms (Fig 3) whereas the same dose range of ouabain had little effect on His bundle rhythms (Fig 4) The difference in the heart rates during A V nodal escape rhythms in the anesthetized dogs as compared to unanesthetized patients is probably due to the use of the anesthetic Nembutal which is atropinic Also the dog has a higher intrinsic heart rate than man [21]

Recently Damato and associates[15] have reported recordings of A V nodal potentials in the dog As was described by Alanis and co-workers[16] and Pruitt and Essex[17] this potential tends to increase in duration and decrease in amplitude under conditions associated with slowed conduction through the A V node i e. atrial pacing and vagal stimulation During induced A V nodal rhythms, Damato and associates found no A V nodal potential preceding His bundle

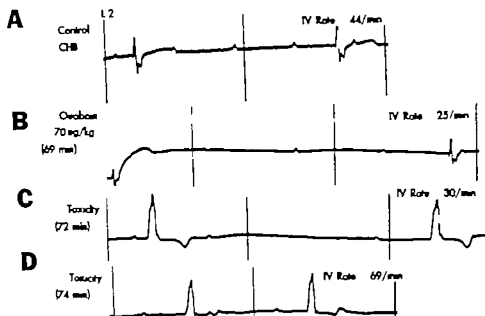


Fig. 5 *A B C*, and *D* Ouabain toxicity during idioventricular rhythm during complete heart block. Lead II of the standard electrocardiogram (*L-2*) is shown in all traces. *A* After the induction of complete heart block, stable idioventricular rhythm at 44/min. was observed. *B* After progressive ouabain injection (cumulative dose 70 µg per kilogram) the idioventricular rate has decreased to 25/min. *C*, Within the next 2 minutes new focus appears at slightly higher rate (30/min) *D* After 2 minutes, this new focus has rapidly increased to 69/min. Within 5 minutes this pacemaker rate was 150/min.

activity They therefore, concluded that the pacemaker in A V nodal rhythm lies within the His bundle. However such negative evidence does not preclude the possibilities that

1 The locus of the A V nodal pacemaker is not at the same site from which the A V nodal potential is recorded.

2 The A V nodal potential[17] is actually part of atrial depolarization.

3 Activity through the A V nodal tissue spreads more slowly during nodal rhythm than during sinus rhythm

In respect to the last of these possibilities, Watanabe and Dreifus,[17] on the basis of microelectrode recordings, have stated that a comparison of action potentials from the A V node in the presence of A V nodal and sinus rhythms showed that during A V nodal rhythm the rate of depolarization as well as the amplitude was often decreased These alterations tend to slow conduction velocity around the site of impulse formation. Exit block can be explained on this basis.

Whether the locus of the A V nodal rhythm lies in the functional A V node or elsewhere, e.g coronary sinus, the evidence presented above indicates that there are at least two areas of latent rhythmicity in the region of the A V node and His bundle. Also these pacemakers respond chronotropically in a consistent qualitative and quantitative fashion to the acute administration of ouabain.

Our findings also confirm those previously reported by Vassalle, Greenspan and Hoffman who observed that the administration of ouabain caused a progressive slowing of the sinus rate in dogs anesthetized with sodium pentobarbital however just prior to toxicity the rate of the sinus pacemaker consistently increased to control levels or greater A recent report by Ten Eick and Hoffman[19] has demonstrated that the negative chronotropic effect of cardiac glycosides on the mammalian sinus node is entirely related to digitalis alteration of the neural control of the pacemaker A similar effect on A V nodal rhythms

might be likely but has not as yet been reported

Vassalle Greenspan and Hoffman[2] found as in the present study that the rate of idioventricular pacemakers in complete heart block was depressed by ouabain. They suggested that this depression of idioventricular foci by ouabain may explain at least in part the well documented antiarrhythmic action of digitalis clinically. However it might be questioned whether digitalis would depress ventricular premature beats induced by injury in the same manner as it suppresses the automaticity of idioventricular rhythms produced by inactivation of higher automatic centers. It has been shown that ventricular arrhythmias will occur more readily in the digitalized heart in response to direct current (D C) shock.[19] A differential response of idioventricular pacemakers to digitalis can be inferred from the fact that digitalis-induced ventricular arrhythmias show a different focus than the ventricular escape focus seen after vagal arrest of supraventricular pacemakers[1,20] or idioventricular foci during complete heart block.

In regard to the effects of high doses of ouabain on idioventricular pacemakers, Vassalle Greenspan and Hoffman[2] found an enhancement of idioventricular automaticity. Our findings clearly indicate that the advent of ouabain toxicity during idioventricular rhythms was characterized by the abrupt appearance of a new focus from that seen after the production of complete heart block. Furthermore the appearance of this toxicity pacemaker occurred in two distinct phases. In the initial phase the new focus beat at the same rate or at a slightly higher heart rate than the original focus. This initial appearance of the new automatic focus seemed transient since it consistently disappeared for one to three minutes and then abruptly reappeared at a faster rate which rapidly accelerated and established a stable ventricular tachycardia (Fig 5).

Summary

The influence of ouabain on various spontaneous and experimentally induced cardiac rhythms was determined. Twenty three mongrel dogs anesthetized with sodium pentobarbital (30 mg per kilogram) were digitalized by the administration of ouabain 10 µg per kilogram every 10 minutes until toxicity developed. A Lead II electrocardiogram His bundle electrogram and aortic blood pressure were continuously monitored. During sinus rhythm (average HR 157 ± 25 beats/min) the rate of this pacemaker steadily declined in response to ouabain then abruptly increased prior to the onset of toxicity (ventricular tachycardia). During A-V nodal rhythms induced by crushing or cooling the S A node in 11 dogs, the average heart rate was 94 ± 22 beats/min. Progressive digitalization consistently decreased the A-V nodal rate (average −44 per cent) until toxicity developed. His bundle (average HR 39 ± 9 0 beats/min) or idioventricular rhythm (average HR 42 ± 5 2 beats/min) with complete heart block was induced by the local injection of 0.3 to 0 5 c.c. of formaldehyde into the A V nodal or His bundle region respectively. Progressive digitalization produced no significant change in the rate of the His bundle pacemaker whereas ouabain consistently decreased the idioventricular rate (average −50 per cent). We conclude that ouabain exerts distinctly different chronotropic effects on various cardiac areas exhibiting automaticity. These differential effects on A-V nodal and His bundle rhythms suggest the existence of at least two areas of latent pacemaker activity which are anatomically contiguous but functionally distinct.

We thank Jorge Rodriquez, Israel Dingle and Octavio Suarez for their technical assistance as well as Miss Mary Ann Westbury for her aid in the preparation of this manuscript.

REFERENCES

1. Vassalle, M, Greenspan, K. and Hoffman, B. F.: An analysis of arrhythmias induced by Ouabain in intact dogs, Circ. Res. 13:132, 1963.
2. Vassalle, M, Greenspan, K. and Hoffman, B. F.: Ouabain toxicity in complete heart block, Fed. Proc. 21:134, 1962.
3. Schafer, H. H., Witham, A. C. and Burch, J. H.: Digitalis tolerance and effect of Acetyl-Strophanthidin upon serum potassium of dogs with acidosis and uremia, AMER. HEART J. 60:388, 1960.
4. Lown, B. and Levine, S. A.: Current concepts in digitalis therapy, New Eng. J. Med. 250:771, 819, 866, 1954.
5. Mendez, C., and Me[illegible]

adrenergic cardiac acceleration by cardiac glycosides, J Pharmacol. 131 191 1961.
6. Hoffman, B. F and Singer D H. Effects of digitalis on electrical activity of cardiac fibers, Progr Cardiovasc. Dis. 7:226, 1964
7. Scherf D and Cohen, J Atrioventricular rhythms, Progr Cardiovasc. Dis. 8:499 1966.
8. Hoffman, B. F Physiology of the conduction mechanism, Ann N Y Acad. Sci. 3:967 1964.
9. Scherlag, B. J Kosowsky B. D and Damato, A N A technique for ventricular pacing from the His bundle of the intact heart, J Appl. Physiol. 22:584 1967
10. Scherlag, B. J Helfant, R. H., and Damato, A. N A catheterization technique for His bundle stimulation and recording in the intact dog, J Appl. Physiol. 25:425 1968.
11. Lister J W Hoffman, B F and Kavaler F Reversible cold block of the specialized cardiac tissues of the unanesthetized dog, Science 145 723 1964.
12. Hoffman, B. F Moore, E. N Stuckey J H., and Cranefield, P F Function properties of the trioventricular conduction system, Circ. Res. 13:308, 1963
13. Mendez, C., Han, J Garcia de Talon, P D and Moe, G. K. Some characteristics of entricular echoes, Circ. Res 16:562, 1965
14. Coraboeuf E De Loze, C., and Boestel, J.: Action de la digitale sur les potentiels de membrane et d'action d tissu conducteur d coeur de chien etudiée l'aide de microelectrodes intracellulaires, C. R Soc Biol. 147 1169 1953.
15. Sano, T Tsuchihashi, H., and Shimato, T Electrical activity of single cardiac muscle fibers and theory of electrocardiography I Electrical activity of single cells, Tokyo, 1960 Igak Shoin, Ltd.
16. Moore, E. N Jomain S. L Stuckey J H., Buchanan, J W and Hoffman, B F Studies on ectopic trial rhythms in dogs, Amer J Cardiol. 19:676, 1967
17. Watanabe, Y and Dreifus, L. S. Sites of impulse formation within the trioventricular junction of the rabbit, Circ. Res. 22 717 1968.
18. Cranefield P F Hoffman, B F and Paes De Carvalho, A Effects of acetylcholine on single fibers of the trioventricular node, Circ. Res. 7 19 1959
19. Paes De Carvalho, A.: Excitation of the trioventricular node during normal rhythm. Effect of acetylcholine, in Dreifus, L. S., and Likoff W editors: Mechanisms and therapy of cardiac arrhythmias, New York, 1966 Grune & Stratton, Inc., p. 341.
20. Narula, O. S Scherlag B J and Samet P His bundle blocks and His bundle rhythms, Dis. Chest. 56:238, 1969
21. Narula, O S., Scherlag, B J J vier R. P Hildner F J and Samet, P.. Analyses of A V conduction defect in complete heart block utilizing His bundle electrograms, Circulation 41:437 1970.
22. Narula, O S. Unpublished observations.
23. Scherlag B J Yeh, B K., Abelleira, J L and Samet, P Differentiation of middle, lower A V nodal and His bundle rhythms in the dog Fed. Proc. 29:587 1970.
24. Spector W S.. Handbook of biological data, Philadelphia and London, 1956, W B Saunders Company p. 277
25. Damato, A. N Lau, S. H Bobb, G. A Steiner C., and Wit, A. L. Recording of A V nodal activity in the intact dog heart, Physiologist 12:203, 1969
26. Alanis, J Lopez, E., Mandoki, J J and Pilar G. Propagation of impulses through the trioventricular node, Amer J Physiol. 197 1171 1959
27. Pruitt, R. D and Essex, H. E. Potential changes ttending the excitation process in the trioventricular conduction system of bovine and canine hearts, Circ. Res. 8 149 1960.
28. Ten Eick, R. E., and Hoffman, B. F.. Chronotropic effect of cardiac glycosides in cats, dogs and rabbits, Circ. Res. 25:365, 1969
29. Lown, B Kleiger R., and Williams, J Cardioversion and digitalis drugs. Changed threshold to electric shock in digitalized animals, Circ. Res. 17:519 1965
30. Helfant, R. H., Scherlag, B J and Damato, A. N.. Electrophysiological properties of diphenylhydantoin sodium (Dilantin) in the normal and digitalis intoxicated heart, Circulation 36:108, 1967

Reduction of electrocardiographic beat to-beat variation through computer wave recognition

K Ishikawa M D
C Batchlor M S
H V Pipberger M D
Washington D C

It is well known that both beat to-beat and observer variation represent limiting factors for the accuracy and reliability with which electrocardiogram (ECG) measurements can be taken Their influence has recently been quantitatively evaluated by Fischmann and co-workers[1] They found that easily identifiable points in the electrocardiogram such as peaks of R waves or maximal vectors rarely vary by more than 0 1 mv Considerably larger variations were found for time intervals such as P QRS or Q T durations which depend critically on the accuracy and consistency with which the onset and end of various wave forms are determined Such variations were relatively large both when consistency of measurements was tested between observers and when tested for the same observer at different times Instantaneous vectors, which are frequently used for vectorcardiographic (VCG) diagnosis of myocardial infarcts are usually determined after the beginning or more rarely prior to the end of QRS complexes. Their accuracy depends mainly on finding the exact onset and end of QRS complexes Any shift in time of these points may lead to considerable changes of all succeeding vectors both in amplitude and direction.

The question arises therefore, whether the variability in beat to-beat and observer variation can be reduced when precise mathematically defined criteria, programmed for a digital computer are applied for determination of onset and end of ECG waves. To investigate this question normal and abnormal records from 184 patients were subjected to a computer wave recognition program The results were compared with those obtained by hand measurements as reported previously [1]

Material and methods

A total of 184 corrected orthogonal (Frank system) ECG s were selected from a variety of diagnostic groups in our magnetic tape library (Table I) Since respiration is the most important physiologic variable causing beat to-beat variations (BBV) 7 consecutive heart beats were selected from each record for the calculation of BBV in order to include at least one

From the Veterans Administration Research Center for Cardiovascular Data Processing and Georgetown University School of Medicine Department of Medicine Washington, D. C.

Supported in part by Research Grant HE 09696, National Heart and Lung Institute, United States Public Health Service.
Received for publication April 14, 1970.

Reprint requests to Dr H V Pipberger Veterans Administration Hospital, 50 Irving St., N W Washington, D C 20422.

Table I

Groups	No. of patients
Normal	45
Hypertensive cardiovascular disease	51
Pulmonary emphysema	36
Myocardial infarction	52
Total	184

respiratory cycle. Thus a total of 1,288 complexes for the 184 cases were used. The records were all reproduced from FM magnetic tape the original ECG's having been recorded at a number of different Veterans Administration hospitals. Total system bandwidth extended from 0.05 to 1,250 Hz with the signal to-noise ratio on the order of 40 decibels. Analogue to-digital conversion of these records was accomplished to a precision of 0.1 per cent at a sampling rate of 1.0 msec. per lead using equipment and techniques described previously

Using automatic wave recognition by digital computer developed previously at this laboratory the beginning and end of the P wave and QRS complex and the end of the T wave were determined. On the basis of this computer program the following measurements were obtained (1) P and QRS duration, P R and Q-T intervals (2) amplitude and duration of individual deflections in each of the three orthogonal leads (3) magnitude and direction of two sets of instantaneous QRS vectors 0.01 0.02 0.03 0.04 and 0.05 sec., both after the onset and before the ending of QRS (4) magnitude and direction of the maximal spatial QRS vectors. The criteria used in automatic wave recognition are spatial velocity values for determining onset and end of P and QRS waves, and spatial magnitude values for determining the end of the T wave. Specific values for these quantities are dependent to a large extent on the noise level present in the particular ECG record and on the sampling rate and precision used in the analogue-to-digital conversion process. A typical value for determining the onset of QRS is 25 μv per milliseconds.

Statistical computation utilized in the study by Fischmann and co-workers have also been used in this paper in order to make possible a comparison of these two studies.

Maximal beat to-beat variation (BBVm) was calculated by the following method The mean from the seven consecutive beats and deviation from the mean were calculated for each case. The deviations were then pooled for the total cases as well as for each group and the 96 percentile ranges and means of the pooled values were tabulated When the pooled data showed normal distribution the mean plus 2 standard deviations was used to express BBVm When the data were not normally distributed, the upper limit of a 96 percentile range was used to express BBVm

Results

BBV of time measurements Fig 1 shows a comparison of mean and maximal beat to-beat variations of time measurements between visual and computer wave recognition techniques. The greatest improvement effected by the computer was in QRS duration measurements where the visual method values of 6 and 19 msec. were reduced to 2 and 7 msec. for mean BBV and BBVm respectively P duration and Q-T interval measurements also were improved when computer wave recognition was applied but the improvements were not as marked as with QRS duration There was almost no difference between the methods for P R interval measurements.

BBV of spatial instantaneous vectors As shown in Fig 2 BBV of instantaneous vectors were generally lower when computer wave recognition was employed. The pattern of higher BBV in the mid temporal vectors was maintained regardless of whether visual or computer wave recognition was used. For all the instantaneous vectors taken as a group mean BBV was reduced from 0.26 mv to 0.20 mv with the use of computer wave recognition No significant differences in BBV between the 2 methods were noted when amplitudes of maximal spatial QRS vectors or R-wave peaks were measured. Table II summarizes

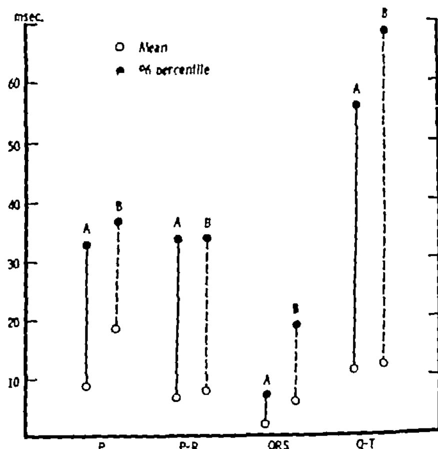


Fig. 1 Comparison of BBV of ECG time measurements determined by computer wave recognition with that by visual wave recognition (A by computer wave recognition B by visual wave recognition) As compared to visual determination BBV (mean and 96 percentile) in P and QRS duration and Q-T interval were significantly reduced by computer wave recognition whereas BBV in P R interval remained almost unchanged.

the relationship between BBV and maximal spatial QRS magnitude for the subjects when broken down into disease categories As clearly demonstrated in this table the hypertensive group had the highest BBVm and the greatest spatial maximal QRS magnitude On the other hand the pulmonary emphysema group had the lowest BBVm and the smallest spatial maximal QRS magnitude the normal and myocardial infarct groups were placed in between

Maximal BBV of direction of spatial vectors Table III presents the BBV of the direction of instantaneous vectors determined with computer wave recognition These values when compared with those obtained using visual wave recognition were considerably reduced for each vector considered With all 10 instantaneous vectors considered as a group the mean value of BBV was reduced from 56 degrees to 16 degrees. Values of BBV for vectors close to the onset or end of QRS tended to be higher than those in the mid temporal region of QRS using either wave recognition method

BBV of amplitude of maximal spatial vector and peak scalar deflection. No significant differences in the BBV for these measurements were noted between visual and computer wave recognition As shown in Fig 2 BBV for these quantities were very low The reason for the similarity of results of both methods is that the same computer program was used to identify peak magnitudes in both this study and that of Fischmann and co-workers.

Discussion

Since the study of Kossmann[4] in 1953 BBV and observer variation have attracted the attention of several investigators.[1,5,6] In spite of this, we believe that not enough emphasis has been given to its significance in routine use of electrocardiog

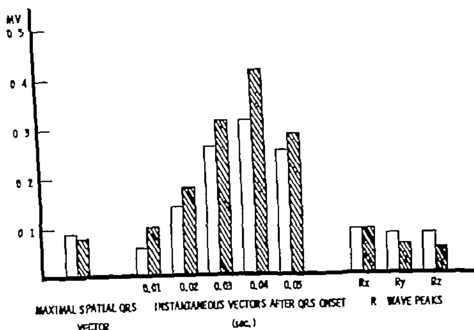


Fig. 2. Comparison of maximal BBV of three groups of ECG measurements obtained by computer wave recognition with that by visual wave recognition technique (Blank column, by computer wave recognition; shaded column, by visual wave recognition). BBV in instantaneous QRS vectors was markedly reduced by computer wave recognition, while there was no essential change in BBV of maximal spatial QRS vector and R-wave peaks.

raphy. As with other sources of error, knowledge and consideration of BBV in the ECG should lead to a better interpretation of the electrocardiogram. BBV may be categorized as those arising from physiologic variations such as respiration, autonomic nervous control, and change in body position, and those caused by technical errors in the measurement of amplitudes and durations. The most important of the technical errors are those of recognition of beginning and end of waves. As can be seen in Fig. 1, the computer wave recognition could reduce the BBV in of QRS duration to one third of that determined by visual wave recognition. The BBV of QRS duration was the smallest of any other time measurements examined both in this study and the previous study by Fischmann and associates. This may be due to the fact that the rate of amplitude change is greater at the onset and end of QRS than at any other wave points. This marked reduction in BBV of this term can be of great value in the diagnosis of ventricular conduction defects. The computer technique could not improve upon the BBV of P-R intervals. Both automatic and visual wave recognition appear to have the same difficulty in identification of the beginning of P waves. Since the onset of the R wave could be identified with considerable consistency by both techniques, less accuracy in the determination of onset of P waves appears mainly responsible for the BBV of P-R interval. The BBV in the measurements of P duration could be substantially reduced by computer wave recognition. The superiority of the computer was evident for identification of the end of the P wave. The Q-T interval has the largest BBV of the time measurements (Fig. 1). The computer technique, however, could substantially reduce the range of this BBV, although not to the same degree as the measurements of QRS duration. Mean and 96 percentile range of the BBV in the R-R interval were 15 msec. and 62 msec., respectively, which were, as can be seen in Fig. 1, almost identical with those

Table II. BBVm of the spatial instantaneous QRS vectors

Groups	Range (sec.)	Mean (sec.)	Maximal spatial vector magnitude (mv.)
HCVD	0.07–0.38	0.26	1.93
Normal	0.07–0.31	0.19	1.53
MI	0.06–0.24	0.17	1.43
PE	0.06–0.22	0.16	1.23

Abbreviations: HCVD = Hypertensive cardiovascular disease; MI = myocardial infarction; PE = pulmonary emphysema.

Table III. Mean and mean + 2 S.D. of beat-to-beat variation of the direction of instantaneous spatial QRS vectors

Instantaneous QRS vectors (sec.)	After onset of QRS		Before end of QRS	
	Mean	Mean + 2 S.D.	Mean	Mean + 2 S.D.
0.01	6 (25)	21 (77)	8 (28)	26 (78)
0.02	6 (17)	24 (57)	4 (25)	16 (83)
0.03	4 (16)	16 (52)	3 (17)	11 (63)
0.04	3 (11)	11 (37)	3 (14)	11 (46)
0.05	3 (9)	9 (27)	3 (13)	13 (43)

S.D. = Standard deviation.

of the Q-T interval. As a result, it can safely be assumed that the large BBV of the Q-T interval is mainly due to the BBV in the R-R interval.

The diagnostic usefulness of instantaneous vectors in VCG diagnosis, especially for myocardial infarction has been stressed by many investigators. Automatic wave recognition as used in this study can markedly reduce the range of BBV of spatial instantaneous QRS vectors as shown in Fig. 2.

Table III shows that a higher magnitude of spatial maximal QRS vector is associated with a larger BBV of spatial instantaneous QRS vector. When the amplitude of spatial instantaneous QRS vectors is used for the establishment of a certain diagnosis, it should be kept in mind that the BBV of these quantities are highly dependent upon the magnitude of spatial maximal QRS vectors. Thus in hypertensive patients with high voltage QRS complexes errors in wave recognition are of greater consequence in the determina- tion of instantaneous vector amplitud- than in emphysema patients. The dire tional BBVm of spatial instantaneous QR vectors could be also substantially reduc by application of computer wave recogr tion. This reduction can also be attribut to greater consistency in the determinati of beginning and end of QRS. The da in Table III summarize these finding Simple amplitude measurements such Q, R, and S waves in scalar leads a magnitude of spatial maximal QRS vect showed the smallest BBV. This observati is in keeping with the previous report l Fischmann and co-workers.

Intra-observer variations have be studied by several investigators includi Fischmann and co-workers.[1] Repeat rec ing variations of P duration for 2 phy sicians, for example, resulted in mean and maximal figures of 12 and 46 msec respectively on a group of 58 records.[1] These inevitable variations in wave recog

ution by human scanning can be significantly reduced when computer wave recognition techniques are used

In clinical applications of ECG computer analysis, the beat to-beat variation can be markedly reduced by using averages. In this laboratory median values over a 6 sec. period are used Such averages become considerably more reliable when the variability of wave recognition techniques for single beats is kept at a minimum.

Summary

In the quantitative analysis of electrocardiograms, beat to-beat variation (BBV) may lead to erroneous interpretation of records. Therefore, it is highly desirable that BBV be reduced as much as possible. Technical errors causing BBV are usually the result of inconsistency in the identification of beginning and end of waves. This study was undertaken in order to test whether the variability in BBV and observer variation can be reduced when precise mathematically defined criteria programmed for a digital computer are applied for determination of onset and end of ECG waves. Normal and abnormal corrected orthogonal (Frank system) ECGs from 184 patients were subjected to a computer wave recognition program Seven consecutive heart beats were selected from each record for calculation of BBV As compared to visual determination of ECG time intervals variation of QRS duration P duration and Q-T interval were markedly reduced by computer technique whereas that of P R interval remained unchanged. Computer wave recognition also significantly reduced BBV in magnitude and direction of spatial instantaneous QRS vectors. In order to achieve greater accuracy in quantitative ECG analysis, application of precisely formulated wave recognition technique appears desirable

REFERENCES

1 Fischmann, E., Cosma, J and Pipberger H. V.. Beat-to-beat and observer variation of the electrocardiogram, Amer. Heart J 75:465 1968.
2. Taback, L., Marden, E., Mason, H. L., and Pipberger H. V Digital recording of electrocardiographic data for analysis by digital computer IEEE Trans Biomed. Engin. 6 167 1959
3. Stallmann, F and Pipberger H. V Automatic recognition of electrocardiographic waves by digital computer Circ. Res. 9 1138, 1961
4 Kossmann, C. E.: Normal electrocardiogram Circulation 8:920, 1953.
5 Acheson, R. M Observer error and variation in interpretation of electrocardiograms in epidemiological study of coronary heart disease Brit. J Prev Soc. Med. 14:99 1960.
6 Segall H N Electrocardiogram and its interpretation. Study of reports by 20 physicians on set of 100 electrocardiograms, Canad. Med. Ass. J 82:2, 1960.
7 Epstein, F H Doyle, J T Pollack, A. A., Pollack, H., Robb, G. P and Simonson, E Observer variation in interpretation of electrocardiograms, J.A.M.A. 175:847 1961
8 Gorman, P A., Calatayud, J B Abraham, S. and Caceres, C. A. Observer variation in interpretation of the electrocardiogram Med. Ann. D C. 33:97 1964.

The primary T wave—a new electrocardiographic waveform*

J A Abildskov M D
*Mary Jo Burgess M D***
Kay Millar M D
Roland Wyatt
Gerhard Baule Ph D
Salt Lake City Utah and
Syracuse N Y

The form of the T wave is influenced by both ventricular activation sequence and intrinsic ventricular recovery properties The information concerning activation sequence contained in the T wave is redundant since it is also furnished by the QRS complex This redundant information may mask T wave features which are directly dependent on recovery properties It is almost certain that the diagnostic utility of the electrocardiogram could be improved if a waveform solely due to ventricular recovery could be obtained This paper reports a method of deriving a wave whose form is mainly due to intrinsic ventricular recovery properties This derived waveform has been designated the primary T wave The theoretic basis and method of deriving the primary T wave and experimental tests of its validity will be presented

Theoretic basis

The theoretic basis of the primary T wave is illustrated in Fig 1 A diagrammatic representation of a recorded QRST is shown and below it the same QRS and its secondary T wave As used in this report the secondary T wave refers to the deflection which would follow a given QRS complex if ventricular recovery properties were uniform The area of the secondary T wave equals the QRS area Subtraction of the QRS and its secondary T from the recorded QRS and T results in a new waveform which has been designated the primary T wave The area of the primary T wave is equal to the ventricular gradient and its form has the general features that Van Dam and Durrer[1] found when they simultaneously activated canine ventricles with high intensity stimuli

The first step required to obtain primary

From the Cardiology Division, Department of Medicine University of Utah College of Medicine, Salt Lake City Utah, and the Department of Electrical Engineering, Syracuse University Syracuse, N Y
Supported by United States Public Health Service Research Grant HE 12551 and HE 12611 Training Grant 1 T1 HE 5875, and grant from the Utah Heart Association.
Received for publication April 27 1970.
Reprint request t J A. Abildskov M D University of Utah Medical Center 50 North Medical Drive Salt Lake City Utah 84112.
*Presented at the 1969 Scientific Sessions of the American Heart Association, Dallas Texas.
**This work was done during the tenure of Established Investigatorship of the American Heart Association.

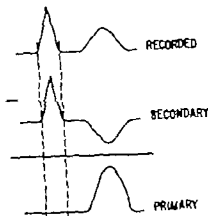


Fig 1 Diagrammatic representations of recorded QRS complex and T wave, the same QRS and its secondary T wave, and the primary T wave. The recorded T waveform is influenced by both activation sequence and intrinsic recovery properties. The secondary T wave is the T wave that would result if all ventricular action potentials were of uniform configuration. The subtraction of the QRS and secondary T wave from the recorded QRST results in an isoelectric QRS and the primary T wave whose form is due to intrinsic recovery properties. The primary T area equals the area of the recorded QRST

T waves is derivation of the secondary T wave A method for calculating the secondary T wave for a given QRS complex was presented in detail in a previous publication[4] and will be summarized here The derivation was based on the form of the downstroke of a diagrammatic transmembrane action potential and the sequence of ventricular activation. The downstroke of the action potential was considered to be related to the T wave in the same way the upstroke is related to the QRS The upstroke can be considered to occur instantaneously and taken to represent the potential difference across the single or limited number of boundaries that exist during a moment of excitation. Because of the relatively long duration of the action potential downstroke multiple boundaries of potential difference exist during recovery The differences in heights of action potentials in adjacent areas were taken to represent the potential differences across the multiple coexisting recovery boundaries. If the heart had uniform recovery properties, the sequence of activation would define not only the geometry of activation wavefronts but also the geometry of boundaries of potential difference during all phases of the recovery process As illustrated in Fig 2 the boundaries exist singly during activation but, during recovery increasing and then decreasing numbers of boundaries of potential difference coexist. Recovery boundaries would appear and disappear in the same order they appeared during activation Instantaneous T amplitude in a given lead could therefore be considered to be related to increasing and then decreasing increments of the QRS area. This relationship of QRS area to instantaneous T amplitude is illustrated in Fig 3 When ventricular action potentials are of uniform configuration the amplitude of initial portions of the secondary T wave are influenced by *increasing* increments of the QRS area, the mid portions of the secondary T wave are influenced by the entire QRS area, and the terminal portions of the secondary T wave are influenced by *decreasing* increments of QRS area. As indicated by the shading of the QRS in Fig 3 both increasing and decreasing increments of QRS are timed from the beginning of the QRS complex. One additional factor namely the difference in slope of the action potential upstroke and downstroke must be considered in the relationship of QRS area to instantaneous T amplitude. If as illustrated in Fig 4 *A* the action potential consisted of an equally abrupt upstroke and downstroke, potential differences across recovery boundaries would equal those across activation boundaries. If as shown in Fig 4 *B* recovery did not occur and no downstroke were present, boundaries of potential differences would be absent during recovery If as shown in Fig 4 C, the downstroke had a slope intermediate between those shown in *A* and *B* the potential difference across a boundary during a single moment of recovery would be less than the potential difference across that boundary during activation. The exact magnitude of potential differences would be related to the slope of the downstroke and if this were constant, potential differences across recovery boundaries would be constant. Since the actual action potential characteristic of ventricular muscle as

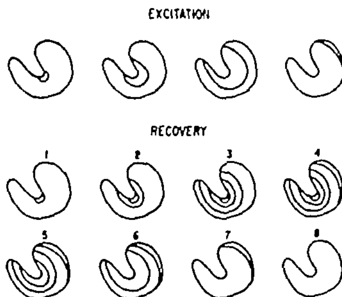


Fig 2 Diagrammatic represent tion of excitation and recovery in a ventricle with uniform recovery properties Four boundaries are shown During excitation the boundaries exist sequentially During the first moments of recovery moments 1 through 3 the boundaries come into exi tence in the same order in which they appeared during excitation During the fourth moment of recovery all of the boundaries are present and during subsequent moments of recovery the bound aries disappear in the same order in which they appeared during excitation and the first moment of recovery

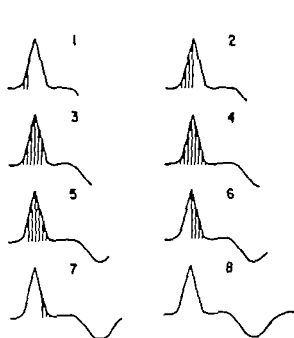


Fig 3 Diagram of the influence of the QRS on secondary T wave amplitude. As indicated by the shading the ampl tudes of the initial portions of the secondary T wave are influenced by increasing increments of the QRS area moments 1 through 3 The peak amplitude of the secondary T wave is influenced by the entire QRS area moment 4 Subsequent moments, 6 through 8 of the secondary T wave are influenced by decreasing increments of the QRS area. Increments of QRS area have been modified by a factor relating the slope of the action potential upstroke and downstroke.

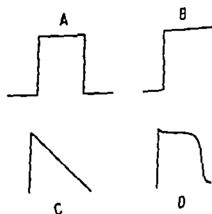


Fig 4 Diagram to illustrate the relation of the slope of the action potential upstroke and downstroke In A the slope of the upstroke and downstroke is the same. With this form of action potential, the potential difference across excitation and recovery boundaries would be the same and the secondary T wave would have the same form as the QRS but opposite polarity In B there is no downstroke W th this circumstance potential differences would not be present during recovery In C the downstroke has a constant slope intermediate between that shown in A and B With this circumstance the moment by moment potential difference across recovery boundaries is consta t during recovery and is less than the potential difference across excitation boundaries. In D an action potential with a form representative of ventricular muscle is shown. The slope of the downstroke is not consta t. W th this circumstance the potential differences across recovery boundaries vary from moment to moment depending on the downstroke slope.

diagrammatically shown in Fig. 4, *D* does not have a constant slope of the down stroke, potential differences across recovery boundaries vary with time. In the observations reported in this paper an action potential with the major features characteristic of ventricular muscle was employed.

The second step in the derivation of primary T waves is the subtraction of secondary from recorded T waves. In this study the onset of secondary T waves was made to coincide with that of recorded T waves. The basis for this operation will be considered in the discussion.

Experimental tests

A variety of ventricular activation patterns were induced and primary T waves derived for each. The test was the degree to which the primary T waves resembled each other and were, therefore, independent of activation order.

Experiments were carried out in 3 dogs anesthetized with pentobarbital, 30 mg per kilogram. The chest was opened in the mid line, the pericardium incised, and the sinus node crushed to permit control of heart rate by electrical stimulation. Bipolar stimulating electrodes were placed on the right and left lateral ventricular walls. The chest cavity was then packed with saline soaked shredded polyurethane foam and the chest wall closed with skin clips. This procedure has been demonstrated to sufficiently restore volume conductor characteristics of the previously opened thorax that spatial electrocardiographic leads can be recorded. The McFee[4] triaxial lead system designed for the dog was used and simultaneous X, Y, and Z Leads recorded at a paper speed of 300 mm per second. QRST area in each lead was obtained by planimetry in one experiment and by electronic integration in the other two. When planimetry was employed, two complexes were each measured three times and the average value taken. With electronic integration, the average of 20 cycles was taken. To minimize variation in wave form, all measurements were made on complexes recorded with respiration halted in a fixed phase of the respiratory cycle. To derive secondary T waves QRS complexes were divided into 10 to 16 parts. Increasing and then decreasing numbers of instantaneous QRS amplitudes were taken to represent increments of QRS area and were used together with a diagrammatic ventricular transmembrane action potential taken from Hoffman and Cranefield. The derivation of secondary T waves was discussed in the section on theoretic basis.

A complexity of these experimental tests was the need to take into account shortened recovery properties near stimulated ventricular sites. This phenomenon was demonstrated by Han and associates,[5] but its physiologic mechanism is unknown. These investigators found that functional refractory periods shortened by 10 msec. for a distance of 10 to 15 mm around a site of ventricular stimulation. Shortening of refractory periods was independent of stimulus strength and occurred with mechanical as well as electrical stimuli.

In the experiments being reported stimuli in various time phases were furnished to sites on both the right and left ventricles. It was postulated that activation of a larger portion of the ventricular mass would result from the stimulus delivered earliest, but alteration of recovery properties associated with ectopic stimulation would occur at both sites. Ventricular gradients differed when right or left ventricular stimuli were applied alone. When both stimuli were applied in various time phases, spatial ventricular gradients clustered in a position between the gradients of independent right and left ventricular stimulation. With stimulation of the right ventricle alone, the position of the ventricular gradient was more toward the right than it was with stimulation of the left ventricle or stimulation of both ventricles. With stimulation of the left ventricle alone the position of the ventricular gradient was more toward the left. This difference in position of the ventricular gradient with right and left ventricular stimulation is compatible with experimental shortening of recovery properties in these areas. These findings indicate that ventricular recovery properties were not the same when stimuli were applied to the right or left ventricles, alone, but recovery prop-

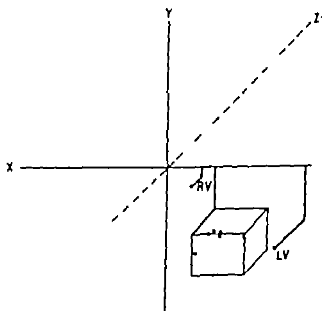


Fig 5 The term m of patial ventricular gradient a sociated with stimulation of a dog s right ventricle (RV) left ventricle (LV) and right and left ventricles n various time phases are shown on a rectangular coordinate system The X Y nd Z axes and position of gradients a sociated w th right and left ventricular stimulation are labeled Stimulatio of both ventricles in var ous t me phases resulted in a cl ter of ventricular gradients in a position between those sociated w th timulation of right and left ventricles alone The spatial coordinates of the gradient a soci ted with left ventricular t mul tion and for a rectangular parallelepiped enclosing the cluster of g dient a sociated with st mi lation of both ventricles are show

erties remained const int when stimuli were applied in various time phases to both ventricles. Findings from one experiment are shown in Fig 5 Primary T waves were derived for the activation orders in which recovery properties remained constant Examples from one experiment are shown in Fig 6 As illustrated there is considerable variation in QRS and recorded T waveform The latter deflections vary from a large upright deflection associated with excitation delivered first to the left and later to the right ventricle to negative deflections when left ventricular stimulation followed right ventricular stimulation after 10 and 15 msec delays Primary T waves while not identical all have the same polarity despite QRS complexes which vary from exclusively negative deflections associated with delayed right ventricular stimulation to largely positive deflections when stimulation of the left ventricle was delayed

Discussion

The theoretic considerations and experimental findings reported here indicate that a new waveform which we have designated the primary T wave is less dependent on activation sequence and more indicative of intrinsic ventricular recovery properties than the recorded T wave The information concerning ventricular activation sequence contained in recorded T waves is redundant and may obscure T wave features which are directly dependent on ventricular recovery Alterations of ventricular recovery are well known manifestations of cardiac disease and a waveform intrinsically dependent on recovery seems almost certain to have diagnostic value

The primary T wave as reported here is closely related to the QRST area or ventricular gradient The ventricular gradient is also independent of activation order if recovery properties are constant but it is a single quantity which does not uniquely describe a waveform The primary T wave can be considered to describe variations of the ventricular gradient as a function of time The latter concept of the gradient as a quantity varying with time was presented by Burch Abildskov and Cronvich [14] in 1954 At that time the concept was illustrated by relating instantaneous QRS and T amplitudes but a physiologic basis for

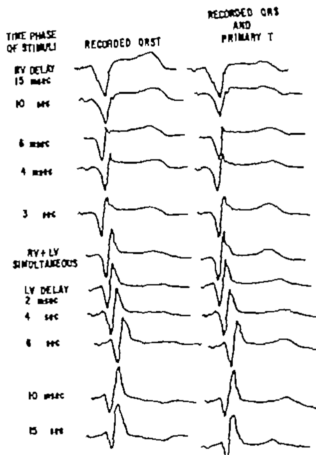


Fig. 6. Recorded ECG of dog resulting from various stimulation patterns are show on the left, and the same QRS complexes and primary T waves are show on the right of the figure. The primary T waves associated with all activation patterns are more alike than the recorded T w es, indicating that primary T waveform is due mainly t intrinsic recovery properties.

this relation was admittedly lacking Since then, the relation of QRS to T waveform has been defined in more precise terms and provides the physiologic basis for determining variations of the gradient with time or the primary T wave

The primary T wave is also closely related to the T wave which would follow simultaneous ventricular excitation. The latter deflection would be totally dependent on intrinsic recovery properties. If the time phase in which to subtract secondary from recorded T waves could be specified for a given case, the primary T as reported would be identical to that following simultaneous excitation The T wave following simultaneous ventricular excitation could be either longer or shorter than recorded T waves, but the durations of these waves could not differ by more than the ventricular conduction time Relationships involved are diagrammed in Fig 7 Diagrammatic ventricular action potentials are shown and the shading indicates the T duration that would result. In Fig 7 *A* the first action potential has the longer duration. Simultaneous onset of both action potentials increases the duration of the T wave. In Fig 7 *B* the first action potential has the shorter duration and simultaneous onset *of both action* potentials decreases the duration of the T wave. Physiologic data indicate that in normal ventricles action potentials of shortest duration are located in the middle layers.[1] Simultaneous activation of normal ven-

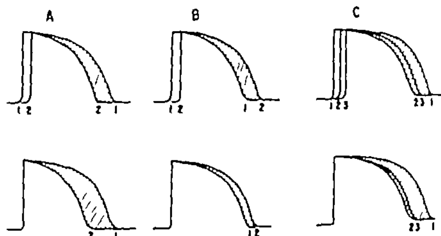


Fig 7 Diagrammatic ventricular action potentials are shown and the shading indicates the duration of resultant T waves. The action potential at the top of the figure have sequential onsets and those at the bottom have simultaneous onsets In A the first action potential has the longer duration, and simultaneous onset increases the T duration. In *B* the first action potential has the shorter duration and simultaneous onset decreases the T duration In *C* three action potentials are shown. The first action potential is the longest and represents endocardial action potentials. The second action potential is the shortest and represents action potentials from middle layers of the ventricles. The third action potential has an intermediate duration and represents epicardial action potential Simultaneous onset of these action potentials results in a T wave with a duration one half a QRS longer than the T wave that resulted with sequential onset of these action potentials.

tricles would be expected to result in T waves starting a half QRS duration before the recorded T wave and ending at the same time as the recorded T wave This relationship is illustrated in Fig 7 C Since the exact time phase in which subtraction of secondary from recorded T waves cannot be determined and T waves resulting from simultaneous ventricular excitation may be either longer or shorter than recorded T waves subtraction was done with the onset of secondary and recorded T waves aligned

Although the primary T wave as described is not identical with the T which would follow simultaneous excitation the experimental data indicate it is less influenced by activation order than the recorded T wave The actual diagnostic value of the deflection can only be established by clinical studies in which its form is correlated with specific states and pathologic findings.

Summary

An electrocardiographic waveform which is largely dependent on intrinsic properties of ventricular recovery and less dependent on activation order than the recorded T wave has been derived This wave has been designated the primary T wave and was obtained by subtracting the secondary from the recorded T wave The secondary T wave was defined as the waveform that would follow a given QRS complex if ventricular recovery properties were uniform. Experimental evidence that the primary T wave is largely independent of ventricular activation order has been obtained

REFERENCES

1 Van Dam R. T and Durrer D The T wave and ventricular repolarization, Amer J Cardiol 14:294 1964
2 Harumi K. Burgess, M J and Abildskov J A. A theoretic model of the T wave Circulation 34:657 1966.
3 Hoffman, B and Cranefield P Electrophysiology of the heart, New York 1960, McGraw Hill Book Company Inc.
4 Abildskov J A. and Boyle, R S. Further studies of the electrocardiographic effects of experimental myocardial lesion, Amer. Heart J 69 49 1964
5 McFee R. and Parungao, A. A orthogonal lead system for clinical electrocardiography Amer. Heart J 62:93 1961
6. McFee R. and Baule, G A compact rotator integrator for rapidly obtaining spatial parameters of the electrocardiogram in Proc. Long Island Jewish Hospital Symposia on Vectorcardiography Amsterdam 1966, North-Holland Publishing Co.
7 Han J Garcia deJalon, P and Moe, G. K.

fibrillation threshold of premature ventricular responses, Circ. Res. 18:18, 1965.

8. Han, J and Moe, G. K. Personal communication.
9. Burgess, M J Harumi, K and Abildskov J A. Application of theoretic T-wave model to experimentally induced T-wave abnormalities, Circulation 34:669 1966.
10. Burch G. E., Abildskov J A and Cronvich, J A.. A study of the spatial vectorcardiogram of the ventricular gradient, Circulation 9:267 1954.
11. Van Dam, R. T and Durrer D Experimental study on the intramural distribution of the excitability cycle and on the form of the epicardial T wave in the dog heart in situ, Amer. Heart J 61:537 1961

Case reports

Subdiaphragmatic total anomalous pulmonary venous drainage Report of a successful surgical correction

H S Joffe M B Ch.B M Med (Paed)
T G O Donovan F.R C S (Edin) F.R.A C S
B P Glaun M B Ch B M.R C.P D C H
E. Chesler M.D (Rand) M.R C.P (Edin)
V Schrire M Sc Ph.D M.D F.R C.P E F.R C.P F.A C C
Cape Town South Africa

The results of surgery for total anomalous pulmonary venous drainage (TAPVD) have been uniformly poor[1] particularly in the subdiaphragmatic type[2] The latter patients invariably have obstruction to pulmonary venous return and therefore present early deteriorate rapidly and inevitably die unless alleviated surgically[3-7] Since the first reported case of successful correction in 1962 only 6 examples have been documented[8-13]

This paper describes the case of an infant with subdiaphragmatic TAPVD in whom the diagnosis was established by angiography and successful surgical correction was achieved

Case report

This male infant is the first child of healthy parents and the product of a normal full term pregnancy and vertex delivery The birth weight was 3 149 Kg. (6 lb 15 oz.) and the length was 53 7 cm.

Within 3 hr after birth, he became cyanosed and developed respiratory distress. The treatment included oxygen (which raised the arterial pO_2 from 30 to 65 mm. Hg) and an intragastric drip of dextrose and bicarbonate. On the fourth day he developed congestive cardiac failure for which digoxin and furosemide (Lasix) were given. Failure to improve led to his transfer to Groote Schuur Hospital on the ninth day

On admission, he was deeply cyanosed and in heart failure, with tachycardia, a respiratory rate of more than 100 per minute, peripheral edema, and a liver edge palpable 5 cm. below the costal margin. Femoral artery pulsations were markedly diminished There was chest wall retraction, diminished breath sounds, and scattered bilateral crepitations. The heart was not clinically enlarged and there were no bruits, but a gallop rhythm was heard.

A chest x ray (Fig 1 A) showed complete opacification of both lung fields compatible with pulmonary edema, and the cardiac outline could not be defined For technical reasons, an electrocardiogram could not be obtained.

Shortly after admission, he had episodes of apnea and intermittent positive pressure ventilation (IPPV) was initiated using a Bird Mark VIII respirator with infant circle The arterial pH rose from 7 24 to 7.56, pCO_2 fell from 62 to 24.5 mm. Hg and the pO_2 (on IPPV with 100 per cent O_2) was

From the Cardiac Clinic, Groote Schuur Hospital Departments of Medicine, Surgery and Child Health, University of Cape Town and the Cardiovascular Pulmonary Research Group.

Supported in the Department of Medicine by the South African Medical Research Council and the Cape Town City Council, Cape Town, South Africa.
Received for publication Jan. 19 1970.

Reprint requests to H. S. Joffe, University of Cape Town, Cardiac Clinic, Groote Schuur Hospital, Observatory Cape Town, South Africa.

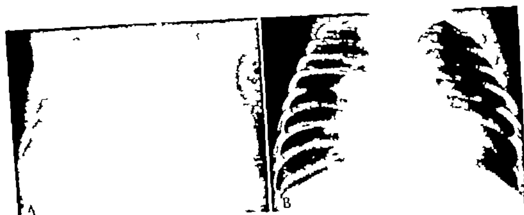


Fig. 1. *A*. Preoperative straight chest x-ray showing gross pulmonary edema and blurring of the cardiac outline. *B*. Eleven weeks after operation showing clearing of lung fields with residual congestion of right lung and normal heart size.

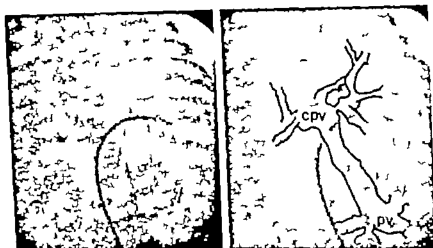


Fig. 2. Pulmonary venous phase of right ventricular cineangiogram in anteroposterior projection. Contrast is seen draining from pulmonary venous branches into common channel which descends to communicate with the portal vein. Gross pulmonary edema obliterates the cardiac outline and the diaphragm. *cpv* = Common pulmonary vein. *pv* = portal vein.

46 mm. Hg. After 24 hours, his clinical condition was much improved and peripheral pulses were more readily palpable but of small volume. The arterial pH was 7.39, the pCO_2 was 24.5 mm. Hg, and the PO_2 was 60 mm. Hg. A second chest x-ray showed slight clearing of the pulmonary edema and normal-sized cardiac outline could be discerned. A diagnosis of TAPVD with obstruction was entertained, but the hypoplastic left heart syndrome could not be excluded.

Investigation was performed with the infant still on IPPV. Cineangiography following injection of contrast medium into the left atrium revealed no abnormality of the left atrium, left ventricle, or aorta. Injection into the right ventricle revealed no abnormality of this chamber or the pulmonary arteries, but the left atrium did not fill in the venous phase. After 3 sec., dye was seen to drain from the pulmonary veins into common venous channel which descended to communicate with the portal vein, confirming the diagnosis of subdiaphragmatic TAPVD (Fig. 2).

Three hours later surgery was performed on cardiopulmonary bypass. Hemodilution (50 per cent blood, 50 per cent electrolyte solution) hypothermia, and circulatory arrest were used. Following median sternotomy gross tissue edema and lung congestion were noted and the right ventricle was hypertrophied. The anomalous pulmonary venous connection was confirmed. Bypass was instituted and the

common pulmonary vein was dissected while the infant was cooled to 20° C and the heart lung machine was stopped. The descending vein was snared and the common pulmonary vein opened with a transverse incision one cm in length. The posterior aspect of the left atrium was opened transversely from the atrial septum to the root of the atrial appendage, an incision of one cm in length. A side-to-side anastomosis was fashioned between the common pulmonary vein and the left atrium using a continuous suture of 5-0 silk. The heart lung machine was restarted and the descending vein ligated inferiorly. Rewarming was uneventful, the heart taking over strongly. Bypass was discontinued and the chest closed with two mediastinal drainage tubes.

Postoperatively the infant was maintained on IPPV administered by endotracheal tube. He survived 2 episodes of cardiac arrest within 2 hours of operation. The lungs cleared progressively over the next 7 days. He then developed gross pulmonary effusions later ... precipitated by left upper lobe pneumonia, *Pseudomonas aeruginosa* being cultured. One week later a second episode of pneumonia in the right upper lobe produced a massive effusion in the right chest. Pseudomonas and Klebsiella aerogenes were cultured from the tracheal aspirate. The treatment included parenteral colistin and gentamicin. He could not be weaned from the respirator until tracheostomy was performed 3 wk. postoperatively. He then improved steadily but evidence of congestion of the right lung persisted. At the age of 11 wk. and at the weight of 4.321 Kg (9 lb. 10 oz.) he was successfully extubated and discharged from the hospital in good health. A follow up x-ray 11 wk. after the operation showed improvement (Fig. 1 B).

Discussion

Total anomalous pulmonary venous drainage (TAPVD) was first described in 1798 in association with other cardiac anomalies[14] and in 1868 as an uncomplicated lesion.[15,16] The unusual variety in which a common pulmonary vein drains into a subdiaphragmatic site was first recorded in 1913 in association with multiple cardiac defects[17] and in 1916 as an isolated entity.[18] Since then many examples from autopsy material have been reported. Burroughs and Edwards identified 188 cases of TAPVD in the literature until 1956 of which 28 drained below the diaphragm.[3] Hastreiter and co-workers[4] described another 37 cases of TAPVD with pulmonary venous obstruction. Clinical recognition of TAPVD has been reported since 1950[19] and surgical correction was first attempted in 1951.[20]

The embryological basis for the development of subdiaphragmatic TAPVD has been presented by Edwards[21] and Neill[22] and requires no elaboration. The uniformly fatal outcome has been ascribed to obstruction of pulmonary venous return with consequent severe pulmonary venous congestion and right heart failure.[3] Several mechanisms for the obstruction have been postulated including the increased resistance offered by the common pulmonary vein as a result of its length or small diameter[4] or from constriction either at the level of the diaphragm[3,23] or at the site of entry into the portal vein, ductus venosus, hepatic veins or inferior vena cava. Drainage into the portal system may also be restricted by arborization of veins within the liver[11,24,25] or by persistent higher relative pressures in the portal system as found in fetal life.[26,27] It seems likely that the anatomical arrangement and degree of restriction govern the clinical presentation, death occurring at any time between 3 days and 4 months.[3,4,27]

Characteristically the patient presents with dyspnea, cyanosis, and congestive cardiac failure and the radiological features of severe pulmonary congestion with a normal-sized heart.[4,28,29] Llewellyn and associates[12] advise operation on the basis of these findings without further investigation. We consider angiocardiography to be essential before surgery to exclude the hypoplastic left heart syndrome and to identify the site of obstruction. The case presented in this paper manifested gross pulmonary edema on the plain film so that the cardiac outline was obscured and accurate evaluation of cardiac size was rendered impossible. In addition depleted venous return to the left heart possibly aggravated by restricted atrial communication or reduced cardiac output from severe cardiac failure resulted in poor peripheral pulses. The hypoplastic left heart syndrome therefore could not be excluded on clinical grounds. Furthermore it is now recognized that a patient with TAPVD into a supracardiac vein may also have pulmonary venous obstruction resulting in an identical clinical and radiological presentation.[29,30] The exact anatomy should therefore be identified before surgery.

The present case illustrates that limited investigation can be performed even on a

Table 1 Clinical and surgical factors in cases of subdiaphragmatic TAPVD successfully corrected by surgery

Investigators of cases	*Age at onset of severe symptoms*	*Age at investigation*	*Age at surgery*	*Closure of ASD/ PFO*	*Ligation of DCVP*	*Postoperative course*
Sloan et al	7 day	11 days	12 days	Yes	Yes	Satisfactory
Cooley and Balas†	Not recorded	7 wk.	7 wk.	Yes	Yes	Satisfactory
Woodwark et al.	3 wk.	6 wk.	6 wk.	N	No	Satisfactory
Jegier et al.	5 days‡	5 days	6 days	N	No	Satisfactory
Llewellyn et al.	6 day	Not performed	12 day	No	Yes	Satisfactory
Mody et al.	4 wk.§	3 wk.	5 wk.	Yes	Yes	Minor complication
Present case	3 hr	11 day	11 days	N	Yes	Complicated

ASD = Atrial septal defect; PFO = patent foramen ovale; and DCPV = descending common pulmonary vein.
Also enlarged left atrium with Teflon graft.
†Cooley and Balas describe another successful operation in an infant of one month, who died [illegible] months later from stenosis of the anastomosis.
‡Transient episode of cyanosis at 6 hours, responding rapidly to oxygen administration.
§Rapid respirations noted soon after birth.

critically ill child The associated acid-base disturbances and ventilatory insufficiency resulting from profuse pulmonary edema must be controlled by adequate blood gas monitoring and IPPV if necessary This service can best be provided by a neonatal intensive care unit.

The surgical technique used is the same as that advised by Cooley and co-workers[1,9] whereby the common pulmonary vein is anastomosed to the posterior wall of the left atrium and ligated distally in its caudal course. The patent foramen ovale was not closed theoretically to provide an escape route if the left atrial capacity were too small to cope with the increased flow There is conflicting opinion as to the advisability of ligation of the descending vein and closure of the PFO (atrial septal defect) [8] and there is as yet insufficient data for evaluation. The age at presentation and variations in technique in the 7 successfully corrected cases are outlined in Table 1

The stormy postoperative course in this patient was probably due in part to the marked degree of pulmonary venous obstruction as judged by the early onset and the severity of the clinical presentation Pulmonary edema is the most frequent complication following repair of TAPVD and may be due to absolute[11] or relative inadequacy of left atrial capacity or to an inadequate anastomosis. The recurrence of right-sided pulmonary congestion in our case suggests residual partial obstruction of the right pulmonary vein.

Summary

The seventh reported case of successful surgical correction of total anomalous pulmonary venous drainage with subdiaphragmatic obstruction is presented Angiographic confirmation of the diagnosis and identification of the site of obstruction was obtained prior to operation. Adequate investigation in a moribund infant was facilitated by the use of intermittent positive pressure ventilation. Surgical correction was achieved by anastomosis of the common pulmonary vein to the left atrium followed by ligation of the anomalous connection to the portal system. Early investigation of these critically ill infants is advocated, since without surgical intervention, the prognosis is hopeless.

We wish to thank Dr T Love of the Department of Anaesthetics, Red Cross Children's Hospital, for his assistance in postoperative care, and the Medical Superintendents of Groote Schuur and Red Cross Children Hospitals, respectively for permission to publish.

REFERENCES

1. Cooley D A Hallman G L and Leachman, R D Total anomalous pulmonary venous drainage. Correction with the use of cardio-

pulmonary bypass in 62 cases J Thorac Cardiovasc. Surg 51:88 1966

2. Mustard W T., Trusler G A., and McLennan T A Total anomalous pulmonary venous drainage in the first six months of life in Cassels Donald E. editor Heart and circulation in the newborn and infant New York, 1966, Grune & Stratton Inc p 339
3. Burroughs, J T and Edwards, J L. Total anomalous pulmonary venous connection, AMER. HEART J 59:913 1960
4. Ha treiter A R Laul M H Molthan M E. and Miller R A Total anomalous pulmonary venous connection with severe pulmonary venous obstruction, Circulation 25:916, 1962
5. Johnson, A. L W lesworth F W Dunbar J S Siddoo, S. and Grajo M Infradiaphragmatic total anomalous pulmonary venous connection, Circulation 1 :310 1958
6. Lucas, R. V Jr Adam I Jr Anderson R. C Varco, R L. Edwards, J E and Lester R. G : Total anomalous pulmonary venous connection to the portal venous system a cause of pulmonary venous obstruction, Amer J Roentgen. 86:561 1961
7. Snellen H A. and Bruins, C Anomalies of venous return in Watson Hamish editor Paediatric cardiology London 1968 Lloyd Luke (Medical Book) Ltd pp. 417 436.
8. Sloan H MacKenzie J Morris, J D Stern A. and Sigmann J Open heart surgery in infancy J Thorac. Cardiovasc. Surg 44:459 1962.
9. Cooley D A. and Balas P E. Total anomalous pulmonary venous drainage into inferior vena cava report of successful surgical correction, Surgery 51 798 1962
10. Woodwark C M A ore D J and Ashmore P G. Total anomalous pulmonary venous return to portal vein J Thorac Cardiovasc. Surg 45:662 1963
11. Jegier W Charrette E. and Dobell A. R C Infradiaphragmatic anomalous pulmonary venous drainage normal haemodynamics following operation in infancy Circulation 35:396 1967
12. Llewellyn M A Cullum, I A Thomas, J B and Anderson I M Infracardiac total anomalous pulmonary venous drainage Brit. Med. J 3:35 1968
13. Mody M R Gallen, W J and Lepley D Total anomalous pulmonary venous drainage below the diaphragm successful surgical correction in an infant Amer J Cardiol 4:375 1969
14. Wilson J A description of a very unusual formation of the human heart, Phil. Tr Roy Soc. London 88:316 1798
15. Friedlowsky A Vrtljschr Prak Heilk. 25:45 1868. Cited in reference 16.
16. Brody H Drainage of the pulmonary veins into the right side of the heart, Arch. Path. (Chicago) 33:221 1942.
17. Rivet L., and Girard L. Un cas de malformation cardiaque avec anomalies multiples de l appareill circulatoire Arch. Mal. Coeur 6:[illegible] 1913.
18. Chon A Ein beitrag zu den anomalien der pulmonalvenen Beitr Path. Anat. 61:[illegible] 1916.
19. Friedlich A. Bing R. J and Blount, S. G Jr Physiological studies in congenital heart disease. IX Circulatory dynamics in the anomalies of venous return to the heart, including pulmonary arterio-venous fistula Bull. Hopkins Hosp. 86:20 1950.
20. Muller W H The surgical treatment of transposition of the pulmonary veins, Ann. Surg 134:683 1951
21. Edwards, J E. Pathologic and developmental considerations in anomalous pulmonary venous connection, Proc. Mayo Clin. 28:441 1953.
22. Neill C. A. Development of the pulmonary veins, Pediatrics 18:880, 1956.
23. Russell V L., Jr Adams, P., Jr Anderson R. C. Varco, R L. and Lester R. G Total anomalous pulmonary venous connection to the portal venous system, Amer J Roentgen. 86:136, 1960.
24. Gott V L. Lester R. G Lillehei, C. W and Varco, R. L : Total anomalous pulmonary venous return An analysis of 30 cases, Circulation 13:543 1956.
25. Gunteroth W G Nadas, A. S. and Gross R. E. Transposition of the pulmonary veins Circulation 18:117 1958.
26. Sherman F F and Bauersfeld S. R.: Total uncomplicated anomalous pulmonary venous connection, Pediatrics 25:656, 1960.
27. Levin B and White H : Total anomalous pulmonary venous drainage into the portal system Radiology 76:891 1961
28. Harris, G. B C Neuhauser E. B. D and Giedion, A Total anomalous pulmonary venous return below the diaphragm Amer J Roentgen 84 436, 1960
29. Eisen, S. and Elliott L P A plain film sign of total anomalous pulmonary venous connection below the diaphragm, Amer J Roentgen. 102:372 1968.
30. Kauffman, S L. Ores, C N and Andersen, D H Two cases of total anomalous pulmonary venous return of supracardiac type with stenosis simulating infradiaphragmatic drainage Circulation 25:376 1962.
31. Mustard W T Keith J D and Trusler G Two stage correction for total anomalous pulmonary venous drainage in childhood J Thorac. Cardiovasc. Surg 44:477 1962

Simultaneous intermittent right and partial left bundle branch block*

Robert D. Patton, M.D.
James S. Roberts, M.D.
Rochester, N. Y.

Intermittent block of the left or right bundle branch is a well-recognized clinical entity.[1-4] Alternating block of the left and right bundle branches has been described.[5-7] We are unaware of a description of intermittent block of both the left and right bundle branches occurring simultaneously. This interesting electrocardiographic finding forms the basis of this report.

Case report

A 62-year-old Puerto Rican man was admitted with a 3 month history of progressive exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and atypical angina which was predominantly epigastric. One month prior to admission he stopped working when symptoms of left ventricular failure progressed despite therapy with digoxin, 0.25 mg. daily and furosemide, 40 mg. twice a day. He denied prolonged chest pain, palpitations, or diaphoresis prior to admission. There was no history of pre-existing hypertension, diabetes, hyperlipidemia, or heart murmur. His past history and family history were noncontributory.

Pertinent positive physical findings included blood pressure of 170/100 mm. Hg, a heart rate of 100 beats per minute, and a respiratory rate of 36. Venous pulsation was noted to the angle of the jaw with the patient upright. Expiratory wheezes and coarse rales were present bilaterally to the scapulae. The heart was enlarged 2 cm. beyond the midclavicular line and a summation gallop was present. No murmur or rub was noted. There was no enlargement of either the spleen or the liver. A trace of peripheral edema was present.

Laboratory examinations revealed a normal complete blood count, normal blood glucose, urea nitrogen, and electrolytes. Urinalysis was unremarkable except for 100 mg. per cent proteinuria. The cholesterol was 312 mg. per cent. Chest x-ray revealed cardiomegaly and pulmonary congestion. The initial electrocardiogram revealed left axis deviation (LAD) and right bundle branch block (RBBB).

Three days after admission the patient developed frequent atrial and ventricular premature beats, and the initially stable LAD/RBBB became intermittent (see more complete discussion below). Digoxin therapy was discontinued and a temporary demand transvenous pacemaker was positioned at the right ventricular apex. The patient slowly improved on standard medical therapy. Digoxin was resumed but discontinued after the appearance of ventricular bigeminy. The ventricular conduction pattern returned to normal after two days and remained unchanged until discharge.

Electrocardiographic findings. Twelve-lead electrocardiograms were taken during normal conduction and during bundle branch block (Fig. 1). Right bundle branch block is indicated by the RSR' in

From the Cardiology Unit, Department of Medicine, University of Rochester Medical Center and the Strong Memorial Hospital, Rochester, N. Y.

This study was supported in part by Grants HE 5300 and HE 5946 from the National Heart Institute, United States Public Health Service.

Received for publication Jan. 19, 1970.

Reprint requests to: Dr. Robert D. Patton, Cardiology Unit, University of Rochester Medical Center, 260 Crittenden Blvd., Rochester, N. Y. 14620.

*This work was performed during Dr. Patton's Traineeship in Cardiology, Department of Medicine and Dr. Roberts' Internship in Medicine, Strong Memorial Hospital, Rochester, N. Y.

pulmonary bypass in 62 cases, J Thorac Cardiovasc. Surg 51:88 1966
2. Mustard W T Trusler G A and McLennan T A. Total anomalous pulmonary venous drainage in the first six months of life *in* Cassels Donald E. editor: Heart and circulation in the newborn and infant New York, 1966, Grune & Stratton, Inc. p. 339
3 Burroughs, J T and Edwards, J E.: Total anomalous pulmonary venous connection AMER. HEART J 59:913 1960.
4 Hastreiter A R. Paul M H Molthan M E. and Miller R. A. Total anomalous pulmonary venous connection with severe pulmonary venous obstruction, Circulation 25:916 1962
5 Johnson A L. Wiglesworth F W Dunbar J S. Siddoo S. and Grajo, M Infradiaphragmatic total anomalous pulmonary venous connection, Circulation 17:340 1958.
6. Lucas, R. V Jr Adams, P Jr Anderson, R. C. Varco, R L Edwards, J E. and Lester R. G : Total anomalous pulmonary venous connection to the portal venous system a cause of pulmonary venous obstruction Amer J Roentgen. 86:561 1961
7 Snellen H A. and Bruins, C Anomalies of venous return, *in* Watson Hamish editor Paediatric cardiology London 1965 Lloyd Luke (Medical Books) Ltd pp. 417-436.
8 Sloan H MacKenzie J Morris, J D Stern, A. and Sigmann, J Open heart surgery in infancy J Thorac. Cardiovasc. Surg 44:459 1962
9 Cooley D A and Balas, P E. Total anomalous pulmonary venous drainage into inferior vena cava report of successful surgical correction Surgery 51:798, 1962
10. Woodwark C M Vince D J and Ashmore P G : Total anomalous pulmonary venous return to portal vein, J Thorac. Cardiovasc. Surg 45:662 1963
11 Jegier W Charrette E. and Dobell A R. C Infradiaphragmatic anomalous pulmonary venous drainage normal haemodynamics following operation in infancy Circulation 35:396 1967
12 Llewellyn M A Cullum P A. Thomas, J B and Anderson, I M Infracardiac total anomalous pulmonary venous drainage Brit. Med. J 3:35 1968.
13 Mody M R Gallen, W J., and Lepley D Total anomalous pulmonary venous drainage below the diaphragm successful surgical correction in an infant, Amer J Cardiol 24:575 1969
14. Wilson J A description of a very unusual formation of the human heart Phil. Tr Roy Soc. London 88:346, 1798.
15 Friedlowsky A : Vrtljschr Prak. Heilk 25:45 1868 Cited in reference 16.
16. Brody H Drainage of the pulmonic veins into the right side of the heart, Arch. Path. (Chicago) 33:221 1942
17 Rivet L., and Girard L. Un cas de malformation cardiaque avec anomalies multiples de l appareill circulatoire Arch. Mal. Coeur 6:720, 1913
18 Ghon, A. Ein beitrag zu den anomalien der pulmonalvenen, Beitr Path. Anat. 62:175, 1916.
19 Friedlich A., Bing R. J and Blount, S. G Jr Physiological studies in congenital heart disease. IX. Circulatory dynamics in the anomalies of venous return to the heart, including pulmonary arterio-venous fistula Bull. Hopkins Hosp. 86:20 1950.
20 Muller W H The surgical treatment of transposition of the pulmonary veins, Ann. Surg 134:683 1951
21 Edwards, J E. Pathologic and developmental considerations in anomalous pulmonary venous connection, Proc. Mayo Clin. 28:441 1953.
22. Neill C. A. Development of the pulmonary veins Pediatrics 18:880, 1956.
23 Russell V L. Jr Adams, P Jr Anderson, R. C., Varco, R. L. and Lester R. G. Total anomalous pulmonary venous connection to the portal venous system, Amer J Roentgen. 86:436, 1960.
24 Gott V L. Lester R G. Lillehei, C. W and Varco, R. L. Total anomalous pulmonary venous return An analysis of 30 cases, Circulation 13:543 1956.
25 Gunteroth, W G. Nadas, A S., and Gross, R. E. Transposition of the pulmonary veins, Circulation 18:117 1958.
6. Sherman F E. and Bauersfeld S. R. Total uncomplicated anomalous pulmonary venous connection, Pediatrics 25:656, 1960.
27 Levin, B and White H Total anomalous pulmonary venous drainage into the portal system Radiology 76:894 1961
28 Harris, C B C. Neubauer E. B. D and Giedion A Total anomalous pulmonary venous return below the diaphragm Amer J Roentgen. 84:436, 1960.
29 Elsen S. and Elliott, L. P A plain film sign of total anomalous pulmonary venous connection below the diaphragm Amer J Roentgen. 102:372 1968.
30. Kauffman, S. L. Ores, C N and Andersen, D H Two cases of total anomalous pulmonary venous return of supracardiac type with stenosis simulating infradiaphragmatic drainage Circulation 25:376 1962.
31 Mustard W T Keith, J D and Trusler G. Two stage correction for total anomalous pulmonary venous drainage in childhood J Thorac. Cardiovasc. Surg 41:477 1962.

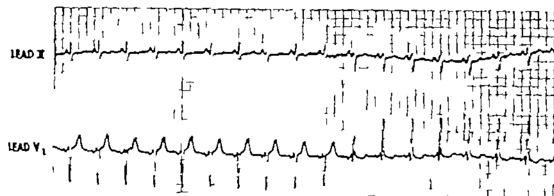


Fig. 3 Simultaneous rhythm strips of Leads II and V showing the simultaneous onset of left axis deviation and right bundle branch block.

of the left bundle branch and the right bundle branch.[8] Anatomic studies of the conduction system in man demonstrates that LAD/RBBB commonly represents involvement of both bundle branches by a variety of pathologic processes.[9-11] Clinical assessment of patients with LAD/RBBB revealed a high incidence of heart block.[12] Left axis deviation occurring in congenital[13] and acquired[14] heart disease has been interpreted as incomplete involvement of the left bundle, providing additional support that LAD/RBBB represents involvement of both bundles. In this patient the criteria for left axis deviation and right bundle branch block were met by the standard electrocardiogram and vectorcardiogram.[15-17] The vectorcardiogram resembles the description of Type A LAD/RBBB reported by Saltzman and his associates.[17] Previous criteria for the electrocardiographic diagnosis of bilateral bundle branch block required demonstration of alternating left and right bundle branch block with varying P-R intervals.[8] We believe that the evidence cited above supports the contention that intermittent *LAD/RBBB* represents bilateral bundle branch block in this patient.

A number of underlying pathologic alterations have been reported to result in bilateral bundle branch block, the most frequent being arteriosclerotic heart disease, aortic valve disease and a degenerative fibrosis of the conduction system.[18] Arteriosclerotic heart disease appeared to be the most probable etiology in this patient with atypical angina. Since the anterior descending branch of the left coronary artery supplies both the anterior division of the left bundle branch and the middle third of the right bundle branch,[9] intermittent ischemia from involvement of this artery could account for the simultaneous intermittent involvement of both bundle branches.

Intermittent left axis deviation, left bundle branch block, right bundle branch block and alternating left and right bundle branch block have been reported.[1,7,18] Intermittent bundle branch block has been precipitated or reversed by changes in heart rate and/or respiration, the Valsalva maneuver, exercise, carotid sinus stimulation, drugs, thyrotoxicosis, open heart surgery, and acute right heart dilatation.[4, 11] Bundle branch block following an atrial premature contraction, as occurred frequently in this patient, has been demonstrated both clinically[4] and experimentally.[22,23] The clinical course is variable. Although the conduction disturbance usually progresses from intermittent to permanent bundle branch block, resolution to normal conduction, as occurred in our patient, has been described.[1]

Summary

A 62-year-old man with presumed atherosclerotic heart disease was found to have *intermittent* LAD/RBBB confirmed by 12-lead electrocardiogram, vectorcardiogram, and two-lead rhythm strips. We believe that this unique electrocardio-

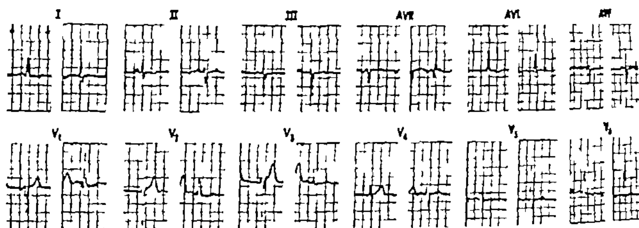


Fig 1 Twelve lead electrocardiogram with normal conduction illustrated on the left and LAD/RBBB on the right. The deep S wave in Lead II and the RSR in V1 best demonstrate the findings.

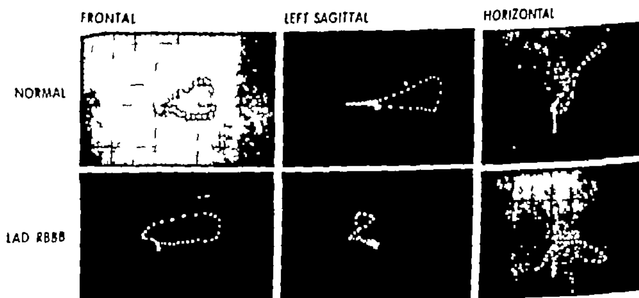


Fig 2 Simultaneous vectorcardiograms demonstrating normal conduction in the top three panels and LAD/RBBB in the bottom three panels. Left axis deviation is manifested by the superior shift of initial forces and right bundle branch block by the shift of late forces to the right with terminal slowing

V and an S wave in the lateral precordial leads Left axis deviation is manifested by a deep S wave in Leads II and III and an R wave in Leads I and aVL. Simultaneous vectorcardiograms likewise reveal shift of the terminal vector to the right and anteriorly with terminal slowing (Fig 2) The initial forces on the frontal and left sagittal planes are shifted superiorly and to the left, consistent with left axis deviation.

Long rhythm strips were taken with simultaneous recordings of Leads II and V1 (Fig 3) Evidence of left axis deviation and right bundle branch block was ... to occur simultaneously At no time

premature atrial beat The basic heart rate was not altered except by the single premature beats. No change was noted with respiration.

Discussion

Both clinical and pathologic data support the thesis that left axis deviation with right bundle branch block (LAD/RBBB) represents bilateral bundle branch block Experimental studies in dogs and baboons have demonstrated that this

An unusual complication of the transvenous pacemaker catheter

R A Massumi M.D
Washington D C

The accidental entry of pacemaker catheters into the coronary sinus and the resultant stimulation of the postero-inferior aspect of the left ventricular epicardium is perhaps one of the most common and best recognized complications of transvenous pacing The pacemaker induced QRS complexes in such cases display a right bundle branch block (RBBB) configuration with the mean vector directed to the right, anteriorly and either superiorly or inferiorly depending on the depth of penetration of the catheter Frequently the catheter fails to pace the heart because of the greatly increased current required for stimulation from this position [1-3] The purpose of this communication is to report a case of coronary sinus pacing in which vigorous and troublesome contractions of the diaphragm occurred intermittently leading to a series of interesting hemodynamic alterations culminating in a significant fall in blood pressure. To our knowledge, this is the first case in which this electrical-hemodynamic interaction has been observed.

Case report

R. B DCGH 249042, an 82 year-old man with complete heart block and Stokes-Adams seizures requiring pacemaker His electrocardiograms over the past year had evolved from pattern of RBBB to complete heart block with RBBB-type QRS (Fig. 1). Recording of His-bundle potentials demonstrated the existence of His-bundle activity after each P wave, thus indicating the presence of bilateral bundle branch block as the basis for the heart block. A temporary pacer catheter inserted into the right ventricle gave rise to left bundle branch block type of QRS (Fig. 1) Two weeks later permanent transvenous demand-type pacer catheter was inserted via the external jugular vein and 1 1 capture was observed. The stimulation threshold was considered to be average and the position of the catheter appeared satisfactory in anteroposterior fluoroscopy to the surgeon. The patient, however noticed vigorous jumping of the stomach synchronous with his heart beats and the electrocardiogram showed RBBB (Fig 1) Chest roentgenograms showed the catheter to be in the posterior vein of the left ventricle (Fig 2) On the following day the volume of the arterial pulse was noted t change from time t time and occasionally become extremely eak even though the pacemaker continued to function properly Careful bedside observation showed that the eakening of the arterial pulse was synchronous ith the ppearance of diaphragmatic contractions, and, that the pulse became strong as soon as the diaphragm ceased t contract. A graphic recording of the brachial arterial pressure simultaneously with Lead V and the sound and displacement tracings of diaphragmatic contractions (Fig. 3) showed that. (1) The arterial pressure was decreased considerably when diaphragmatic contractions were present, with fluctuations i the systolic pressure between a low value of 95

From the Cardiology Division and the George Washington Division of Medicine, District of Columbia General Hospital, Washington, D C 20003
Received for publication Jan. 1 1970.
Reprint requests to: R. A. Massumi, M D., District of Columbia General Hospital, Washington, D. C. 20003.
*Chief Cardiologist, District of Columbia General Hospital, and Associate Professor of Medicine, George Washington University

graphic finding represents simultaneous intermittent involvement of the right and partial left bundle branches

The authors thank Miss Sharon Frederick and Miss Cynthia Stebbins for secretarial assistance. We wish especially to thank Dr. Paul Yu and Dr. Charles Fisch for their critical review of the manuscript.

REFERENCES

1. Bauer G E. Transient bundle branch block, Circulation 29:730 1964
2. Scherlis, L. and Lee Y C Transient right bundle branch block, Amer J Cardiol 11:173 1963
3. Baragan J., Fernandez Caamano, F Coblence B and Lenègre J Intermittent complete left bundle branch block Phonocardiographic and mechanographic study of one case Brit. Heart J 29:520 1967
4. Johnson, K. R. Mullins, C. B Gupta D N and Mitchell J H Effect of intermittent right bundle branch block on right ventricular contractility Amer J Cardiol 17:513 1966.
5. Bourassa M G Boiteau G M and Allenstein B J Hemodynamic studies during intermittent left bundle branch block Amer J Cardiol 10:792, 1962
6. Greico M H Schwartz M J and Chikis, L. P True bilateral bundle branch block Amer J Cardiol 11:666, 1963
7. Hushaw J R. and Linde L M Alternating bundle branch block following heart surgery J Pediat 67:494 1965.
8. Watt T B Jr Freud G E. Durrer D and Pruitt R. D Left anterior arborization block combined with right bundle branch block in canine and primate hearts An electrocardiographic study Circ. Res. 22:57 1968
9. Lenègre, J Etiology and pathology of bundle branch block in relation to complete heart block, Progr Cardiovasc Dis. 6 409 1964
10. Lenègre J Bilateral bundle branch block Cardiologia 48 134 1966.
11. Unger P N Lesser M E. Kugel V H and Lev M The concept of masquerading bundle branch block, Circulation 17:397 1958
12. Lasser R. P Haft, J I and Friedberg C K Relationship of right bundle branch block and marked left axis deviation to complete heart block and syncope Circulation 37:429 1968
13. Guller B DuShane J W and Titus, J. L. The atrioventricular conduction system in two cases of tricuspid atresia, Circulation 40:209 1969
14. Rosenbaum, M B Elizari M V Levi, R J Nau, G J., Pisani, N Lazzari, J O and Halpern, M S. Five cases of intermittent left anterior hemiblock, Amer J Cardiol. 11, 1969
15. Lepeschkin E.: The electrocardiographic diagnosis of bilateral bundle branch block in relation to heart block, Progr Cardiovasc Dis 6:155 1964
16. Castellanos, A. Lemberg L. Ioannides, G and Salhanick, L. The vectorcardiogram in right bundle branch block coexisting with left ventricular focal block, Amer J Cardiol 18:705 1966.
17. Saltzman P Linn, H and Pick, A. Right bundle branch block with left axis deviation, Brit. Heart J 28:703 1966.
18. Unger P Atrioventricular block and cardiac arrest, Second Conference on Coronary Care Units, Rochester N Y., 1969 p. 18.
19. Bauer G. E.: Bundle branch block under voluntary control, Brit. Heart J 26:167 1964
20. Schamroth L. and Bradlow B. A. Incomplete left bundle branch block, Brit. Heart J 26:285, 1967
21. Harrington J F: Reversion of left bundle branch block to normal conduction by carotid sinus pressure, New Eng J Med. 277:37 1967
22. Cohen, S. I., Lau, S. H. Scherlag B. J and Damato, A. N Alternate patterns of premature ventricular excitation during induced atrial bigeminy Circulation 39:819 1969
23. Damato, A. N Lau, S. H Patton R. D Steiner C. and Berkowitz, W D A study of atrioventricular conduction in man using premature atrial stimulation and His bundle recordings, Circulation 40:61 1969



Fig. 2 Posteroanterior and lateral chest roentgenogram showing the position of the catheter tip to be underneath the left ventricle and in direct juxtaposition to the diaphragm (arrow.)

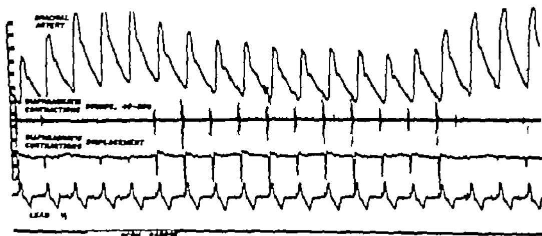


Fig. 3 Brachial arterial pressure recorded simultaneously with sound and displacement recordings of diaphragmatic contractions and with Lead V. To be noted are the cyclic occurrence of diaphragmatic contractions which are clearly visible in the center of the tracing in both sound and displacement recordings. Accompanying these contractions is significant fall in arterial blood pressure and the merging of the P and QRS.

Discussion

The electrocardiographic features and the occurrence of diaphragmatic contractions were consistent with the available information on pacing from the coronary sinus.[3] The fall in blood pressure synchronous with diaphragmatic contractions, on the other hand, is a phenomenon of particular interest.

It cannot be denied that the rise and fall

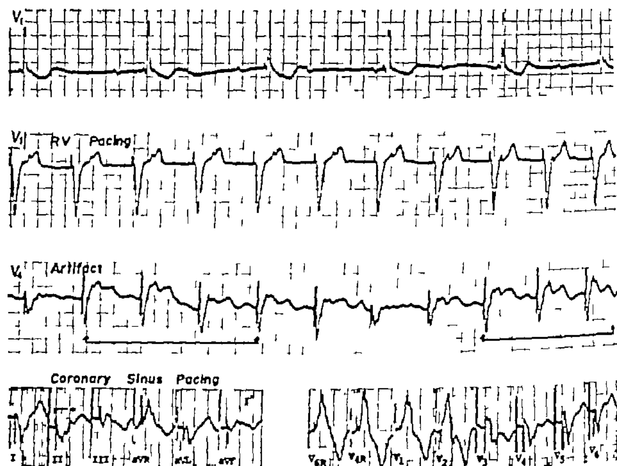


Fig. 1. Electrocardiograms taken before and after insertion of the pacemaker. The top strip shows complete heart block and right bundle branch block which was present on admission. The second strip was recorded after a temporary pacemaker catheter was placed in the right ventricle. The QRS complexes show the expected left bundle branch block. The third strip was recorded in V position after the permanent catheter was inserted. Note mechanical artifacts in the form of giant U waves imparted to the electrocardiogram by diaphragmatic contractions. The bottom strip shows full electrocardiogram including right-sided chest leads when the heart was being paced from the coronary sinus catheter. It shows right bundle branch block with the QRS axis directed superiorly, anteriorly, and to the right.

mm Hg to the high value of 146 mm Hg and (2) the P waves were in front of the QRS complexes when blood pressure was high while they merged with the QRS when blood pressure was low. It was felt that the marked fluctuations in the arterial pressure could not be explained solely on the basis of varying atrial contributions to ventricular filling.

In an attempt to assess the effect on blood pressure of diaphragmatic contractions, the intrathoracic pressure was recorded through a thin polyethylene catheter introduced into the esophagus. Another small catheter was inserted into the femoral vein and pressures were recorded simultaneously with the electrocardiogram and with the displacement tracing of the diaphragmatic contractions. It was noted that during its contractions the diaphragm was thrust downward with great force sufficient to lower intrathoracic pressure by 6 to 8 mm. Hg (Fig. 4). The femoral venous pressure, contrariwise, rose by an average of 4 mm. Hg. It was felt that the sudden, sharp fall in the intrathoracic pressure was causing a trapping or sponging of blood in the pulmonary capillaries and a reduction in venous return to the left side of the heart, a mechanism similar to that observed in deep breathing and in conditions associated with wide fluctuations of the intrathoracic pressure.[4] Furthermore, it was reasoned that the vigorous downward movement of the diaphragm during paced contractions led to an impairment of venous return from the infradiaphragmatic organs.

At cinefluorography of the heart and the diaphragm extremely vigorous diaphragmatic contractions were noted to occur intermittently. The tip of the pacer catheter moved freely within the coronary vein under the diaphragmatic surface of the left ventricle. It was thrust forcefully toward the left ventricular apex whenever the diaphragm was being paced. Observation of the free wall of the right atrium at the same time showed the appearance of giant a waves synchronous with forceful contractions of the diaphragm.

tricular filling The summation of these two effects was the basis for the pronounced fall in arterial blood pressure

REFERENCES

1. Mower M. M., Aranaga, C. E., and Tabatznik, B.. Unusual patterns of conduction produced by pacemaker stimuli, Amer. Heart J 74:24 1967
2. Castellanos, A., Maytin, O Lemberg, L., and Castillo, C.: Unusual QRS complexes produced by pacemaker stimuli with special reference to myocardial tunneling and coronary sinus stimulation, Amer. Heart J 77 732, 1969
3. Barold, S. S Narula, O S., Javier R. P Linhart, J W Lister J W and Samet, P: Significance of right bundle-branch block patterns during pervenous ventricular pacing, Brit. Heart J 31:285 1969
4. Massumi, R. A., Sarin, R., Pooya, M Reichelderfer T R., Fraga, J R., Rios, J C., and Ayesteran, E. Tonsillar hypertrophy airway obstruction, alveolar hypoventilation and cor pulmonale in twin brothers, Dis. Chest. 55 110 1969
5 Nakhjavan, F K., Palmer W H and Mc Gregor M. Influence of respiration on venous return in pulmonary emphysema, Circulation 33:8, 1966.

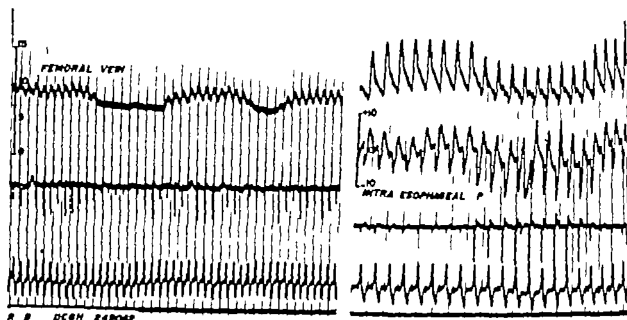


Fig. 4 Left hand panel shows mean femoral venous pressure recorded on top of the panel simultaneously with a displacement tracing of diaphragmatic contractions and Lead V₁ of the electrocardiogram. The right hand panel shows brachial arterial pressure tracings on top, intraesophageal pressure directly below it, a displacement tracing of diaphragmatic contractions, and Lead V. Note the rise in femoral venous pressure and the sharp decline in intraesophageal pressure synchronous with the diaphragmatic contractions. Part of the rise in the mean femoral venous pressure was accounted for by the appearance of giant "a" waves which occurred with the P merged with the QRS. However, the elevation of the mean femoral venous pressure could not be ascribed wholly to the superimposition of the large "a" waves, and it was felt that the rise in pressure reflected an actual impedance to venous return via the inferior vena cava.

of blood pressure coincided with the appearance and disappearance of the P waves before the QRS and therefore reflect at least in part the contribution of atrial filling to the ventricular stroke output. It is improbable, however, that the atrial contribution could account solely for the pronounced fluctuation in blood pressure. It is suggested here that the vigorous diaphragmatic contractions coincident with the giant "a" waves secondary to the merging of the P and QRS played a decisive role in producing variations in blood pressure. The mechanism is viewed as follows. The merging of the P and the QRS led to forceful contractions of the right atrium (giant "a" waves) which in turn caused deep penetration of the catheter tip inside the coronary vein resulting in stimulation of the diaphragm. The latter in turn adversely influenced venous return to the heart both through a sudden increase in the negative intrathoracic pressure impeding venous return from the lung and a sharp increase in intra-abdominal pressure impairing return from the inferior vena cava.

The importance of vigorous diaphragmatic contractions in determining venous return from the vena cava has been demonstrated by Nakhjavan, Palmer, and McGregor.[4] In 6 out of 15 emphysematous individuals, cineangiography of the inferior vena cava showed a marked decrease or complete cessation of flow from the abdominal to thoracic inferior vena cava during inspiration.

Conclusion

Marked fluctuations in the arterial blood pressure were observed in a patient with heart block in whom the pacer catheter entered the coronary sinus and paced the left ventricle continuously and the diaphragm intermittently. The fall in blood pressure was demonstrated to coincide with the periods of diaphragmatic contraction and the merging of the P waves with QRS complexes. It is concluded that the adverse effects of vigorous diaphragmatic contractions on venous return from the lungs and the inferior vena cava were additive to the effects of loss of atrial contribution to ven

Table I Synopsis of cardiac catheterization data at the ages of 5 (1949) and 14 (1958) years

Site	1949		1958 (April)		1958 (November)	
	Pressure	Oxygen content (vol. %)	Pressure	Oxygen content (vol. %)	Pressure	Oxygen content (vol. %)
Right atrium	—	12	—	12 8	—	14 0
Right ventricle	114/0	15 5	105/5	14 9	60/12	18 6
Pulmonary artery	90/60	15 0	—	—	—	—
Femoral artery	—	15 7 (73%)	—	—	—	—
Aorta	—	—	115/88	17 0 (80.6%)	55/40	20.6 (78%)

Examination of the heart showed regular rhythm, left ventricular heave apical thrill, and Grade 3/6 systolic murmur at the left sternal border and over the precordium The edge of the liver was palpable three fingerbreadths below the right costal margin There was no pedal edema and there was 4+ *clubbing of the fingers and toes*

The patient was lethargic The speech was slurred, the tongue deviated to the left and there was peripheral right seventh nerve palsy Paralysis of the left arm and leg, bilateral Babinski and Hoffmann signs, and decreased pain and touch sensation of the left side of the body were evident A lumbar puncture showed grossly bloody fluid with an opening pressure of 18 cm of water During the day of admission, the patient showed progressively increasing lethargy and later he became comatose A lumbar puncture the following day again showed grossly bloody spinal fluid

The hemoglobin value was 23 2 hematocrit 81 per cent, leukocytes numbered 12 000 per cubic millimeter and platelets 50 000 The levels of creatinine and blood urea nitrogen were 2 and 37 respectively each in milligrams per 100 milliliters of blood The concentration of sodium was 138 mEq. per liter The level of fibrinogen was 0 39 Gm per 100 milliliters of blood.

Endotracheal suction yielded moderate amounts of reddish-white mucus The blood pressure remained high at a level of about 180 mm Hg systolic and 140 diastolic

On the following day the patient became unresponsive to pain and there was virtually no urinary output Nasogastric suction yielded coffee ground material Later that day he had respiratory arrest and died

Dr Templeton, will you comment on the angiocardiograms

DR. K T PLATE A forward angiocardiogram on Nov 28 1958 at the age of 14 years, showed dense right-to-left shunt at the level outlining enlarged left ventricle (Fig 2,)

Several days later (Dec 5 1958) retrograde aortography showed the catheter to have passed through transposed aorta into hypoplastic right ventricle (Fig. 2, B) This ventricle seemed to have



Fig 1 Frontal view of thoracic roentgenogram at the age of 14 years.

an inflow portion. Injection of contrast material into the right ventricle showed the pulmonary artery to fill before the aorta, result of extrasystoles. Although the pulmonary valve is not distinctly seen, there appears to be narrow annulus. Both great vessels were transposed but not in inverted positions.

DR. MILES J BUCKER I would now invite Dr Burchell to review the electrocardiograms and to discuss the clinical differential diagnosis.

DR. HOWARD B BURCHELL There are both relatively easy and relatively difficult aspects to the clinical appraisal of this patient s cardiac problem. The story of brain abscess and the final fatal cerebral complication is lamentably a not uncommon story

Clinical pathologic conference

Mies J Becker M D
Kurt Amplat M D
Howard B Burchell M D
Anton I Becker M D
Jesse E Edwards M D
Minneapolis Minn

Case report

DR MILS J BECKER The patient who had been slightly cy notic e nce the ge of two week wa admitted to the Un versity of M nnesota Hospital on five occasions the la t time n 1968 when he w 4 ye rs old

In 1949 t the ge of f v year when first d m tted to the hosp t l the patient w cyanotic The heart w found t be enlarged to th nterior axillary line There w loud (rad 3) tolic murmur which w he rd best n the third nter costal sp ce to the left of the tern m b t transmitted widely nclud ng nto the x lla and back.

The first cardia ath terizat on study i 1949 which is summarized n T ble I wa interpreted indic tive of Eisenmenger yndrome For many years, the patient got al ng well although he had had a number of "colds nd on exercise becam dyspneic and increasingly cyanotic Regularly repeated physical examinations revealed no cha ge n the condition of the heart

In 1957 at the age of 13 years, he was admitted elsewhere because of mening ti and a left parietal brain abscess. The latte was excised and the patie t made a good recovery

One year later (1958) he was readm tted to the University of Minnesota Hospitals for re-ev luation On this admission the roentgenogr (Fig 1) showed an enlarged heart with a very promine t bulge along the left cardia border considered to represent a large left ventricle The pulmonary vasculature was interpreted as with n normal limit Additional catheterization data were obtained n 1958 (Table I)

The patient condition was satisfactory until July 1959 At that t me, he developed seizures with unconsciou nes incontinence, and tongue biting. He was given anticonvul ant medication and had no further seizures through 1960. In November 1961 he noted episodes of dizziness and vertigo but no loss of consciousness. These symptoms recurred on an irregular basis until August, 1964 when a single generalized seizure recurred At that time no change wa noted n cardiac ymptoms or signs. The blood pressure w s 140/100 The frequency of dizzy spells gradually increased and, in 1965 it w noted that these period occurred about once every week This s tuation continued through 1967

In February 1968 the patient wa brought to the hospital because of an episode characterized by dizziness, d plopia, and a tendency to fall to the left Neurologic examination showed bilateral incoordination d plopia on left lateral gaze a right third and seventh nerve paresis, deviation of the tongue to the left, and positive Rhomberg and bilateral Babinski signs. The neurologic consultant felt that basilar artery n ufficiency was the most probable basi for the symptoms. The cardiac findings had not changed from earlier t udies. The patient was discharged from the hospital and remained in his usual tate of health until the morning of May 26, 1968 whe he awoke w th a total left sided paralysis. There wa no headache and he w s alert and oriented Physical exam nation on admission showed a blood pressure of 170/130 a pulse of 76/minute nd a t mperature of 99 8° F The cervical veins were not distended and the lungs were clear to percussion nd auscultation.

From the Department of Pathology The Charles T Miller Hospital, St. Pa l, Minn., and the Departments of Pathology Medicine and Radiology he Univers y of Minnesota, Minneapolis, Minn.

This study as supported by Public Health Service Research Grant 5 RO1 HE05694 and Research Training Grant 5 TO1 HT05570 from the National Heart Institut and by The Netherlands Organization for the Advancement of Pure Research (Z.W O.)

Reprint request t Jesse E Edward M.D The Charles T Miller Hospital, 125 West College Ave., St. Paul, Minn. 55102.

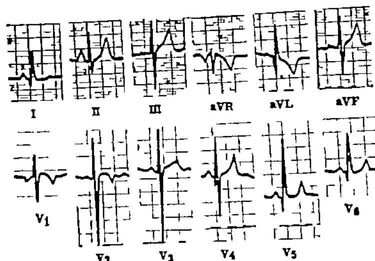


Fig 3 Electrocardiogram at the age of 14 years.

In the items listed above, the loud ejection type murmur and the electrocardiogram are the most important in pointing to tricuspid atresia, with pulmonary stenosis, as the diagnosis. Competing diagnoses, although far down on the list, are (1) an A V cushion defect (complete form of A V commune malformation) with pulmonary stenosis and (2) an underdeveloped right ventricle associated with a large ventricular septal defect and pulmonary stenosis.

As a commentary on advances in diagnosis it is of interest that when the child was catheterized in 1949 (undoubtedly quite early in the experience of the laboratory) an able cardiologist was led astray because of the limited data and pressures recorded and the diagnosis of Eisenmenger's syndrome was made. Throughout the years, the notes indicated the various diagnostic possibilities, but that of tricuspid atresia was usually listed as first choice. A senior pediatric cardiologist early mentioned the likelihood of a single ventricle with transposition of the great vessels and pulmonary stenosis. The angiocardiographic interpretation included a comment on a small right ventricle (Fig 2 *b*) Repeated investigations were not believed warranted as no surgical treatment was believed to have been indicated.

In a search of the records, it is not clear whether or not the catheter ever entered the right ventricle from the right atrium. There are inferences that such occurred but it is not documented.

A feature of interest is the increase with time in the voltage of the P waves in the electrocardiogram, suggesting possible continuing enlargement or hypertrophy of the right atrial chamber (Fig 4) Whether this might reflect changes related only to the passage of time or to the development of increased obstruction to the egress of blood from the right atrium is conjectural.

Thus, the clinical diagnosis on bedside examination with the thoracic roentgenograms and electrocardiogram available should be tricuspid atresia with pulmonary stenosis. When the additional angiocardiographic data are added one can add the diagnosis of transposition of the great vessels.

DR. MIES J BECKER Dr Amplatz, do you wish to make any additional comments on the angiocardiographic interpretation of the right ventricle?

DR. AMPLATZ The configuration of the heart in the frontal roentgenogram (Fig 1) and the hemodynamics in the forward angiocardiogram (Fig 2 *a*) were quite consistent with a diagnosis of tricuspid atresia The selective angiogram (Fig 2 *b*) however was atypical for tricuspid atresia since the inflow portion of the right ventricle was present, which usually is not seen in classical tricuspid atresia. The right



Fig 2 Angiocardiograms at the age of 14 years. a Venous angiocardiogram showing right-to-left shunt at the atrial level and opacification of an enlarged left ventricle b Selective right ventriculogram (through aorta) showing hypoplasia of right ventricle opacification of the pulmonary trunk and pulmonary stenosis.

in patients with venous-arterial shunting of blood On poring over the clinical records on this young man there emerged specific agreed upon findings which are a solid base for logical diagnoses of the physiologic and anatomic abnormalities. These are (1) a prominent systolic thrill and murmur widely distributed over the precordium which should indicate an obstructive lesion at the origin of one or both of the great vessels (2) cyanosis although mild to moderate appeared very early in the patient's life and the situation would reflect a venous-arterial shunt with pulmonary stenosis or a malformation wherein the pulmonary and systemic circuits are separated with poor intermixing that is a malformation associated with transposition of the great vessels (3) the pulmonary vascular shadows in the roentgenograms (Fig 1) were thought to be within the normal range which means that one can accept the fact that the lungs were neither engorged nor markedly oligemic. One can thus conclude that the pulmonary blood flow was reasonably adequate and oxygenated blood in reasonable amounts was being transferred to the systemic circuit The main pulmonary arteries were not enlarged (4) Repeatedly in the clinical records, are notations indicating that the patient, as a child was getting along very well although on exercise he became dyspneic and blue (5) the electrocardiogram done when the patient was 14 years old is the key item in the evidence pointing to a specific anatomic derangement (Fig 3) i e. first the evidence of right atrial enlargement from the high potential of the P waves and second evidence of lack of right ventricular development revealed through absence of anterior and rightward QRS vectors (which features would be characteristic of right ventricular hypertrophy as expected in instances of pulmonary stenosis) it being characterized by a leftward vectorial shift of the QRS in the frontal plane and to the left and backward in the horizontal plane. These electrocardiographic findings strongly point to obstruction at the tricuspid valve and a poorly developed right ventricular chamber

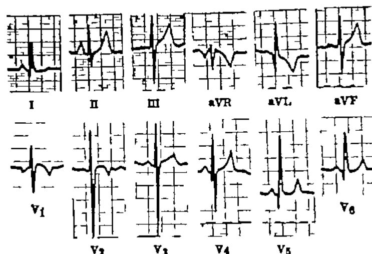


Fig 3 Electrocardiogram t the age of 14 years.

In the items listed above, the loud ejection type murmur and the electrocardiogram are the most important in pointing to tricuspid atresia, with pulmonary stenosis, as the diagnosis. Competing diagnoses, although far down on the list, are (1) an A V cushion defect (complete form of A V commune malformation) with pulmonary stenosis and (2) an underdeveloped right ventricle associated with a large ventricular septal defect and pulmonary stenosis.

As a commentary on advances in diagnosis, it is of interest that when the child was catheterized in 1949 (undoubtedly quite early in the experience of the laboratory) an able cardiologist was led astray because of the limited data and pressures recorded and the diagnosis of Eisenmenger's syndrome was made. Throughout the years, the notes indicated the various diagnostic possibilities, but that of tricuspid atresia was usually listed as first choice. A senior pediatric cardiologist early mentioned the likelihood of a single ventricle with transposition of the great vessels and pulmonary stenosis. The angiocardiographic interpretation included a comment on a small right ventricle (Fig 2 *b*) Repeated investigations were not believed warranted, as no surgical treatment was believed to have been indicated

In a search of the records, it is not clear whether or not the catheter ever entered the right ventricle from the right atrium There are inferences that such occurred but it is not documented.

A feature of interest is the increase with time in the voltage of the P waves in the electrocardiogram suggesting possible continuing enlargement or hypertrophy of the right atrial chamber (Fig 4) Whether this might reflect changes related only to the passage of time or to the development of increased obstruction to the egress of blood from the right atrium is conjectural.

Thus the clinical diagnosis on bedside examination with the thoracic roentgenograms and electrocardiogram available should be tricuspid atresia with pulmonary stenosis. When the additional angiocardiographic data are added one can add the diagnosis of transposition of the great vessels.

DR. MILES J BECKER Dr Amplatz, do you wish to make any additional comments on the angiocardiographic interpretation of the right ventricle?

DR. AMPLATZ The configuration of the heart in the frontal roentgenogram (Fig 1) and the hemodynamics in the forward angiocardiogram (Fig 2 *a*) were quite consistent with a diagnosis of tricuspid atresia. The selective angiogram (Fig 2 *b*) however was atypical for tricuspid atresia since the inflow portion of the right ventricle was present, which usually is not seen in classical tricuspid atresia. The right



Fig 2 Angiocardiograms at the age of 14 years. *a* Venous angiocardiogram showing right to-left shunt at the atrial level and opacification of an enlarged left ventricle *b* Selective right ventriculogram (through aorta) showing hypoplasia of right ventricle opacification of the pulmonary trunk and pulmonary stenosis.

in patients with venous arterial shunting of blood On poring over the clinical records on this young man there emerged specific agreed upon findings which are a solid base for logical diagnoses of the physiologic and anatomic abnormalities. These are (1) a prominent systolic thrill and murmur widely distributed over the precordium which should indicate an obstructive lesion at the origin of one or both of the great vessels (2) cyanosis although mild to moderate appeared very early in the patient's life and the situation would reflect a venous-arterial shunt with pulmonary stenosis, or a malformation wherein the pulmonary and systemic circuits are separated with poor intermixing that is a malformation associated with transposition of the great vessels (3) the pulmonary vascular shadows in the roentgenograms (Fig 1) were thought to be within the normal range which means that one can accept the fact that the lungs were neither engorged nor markedly oligemic. One can thus conclude that the pulmonary blood flow was reasonably adequate and oxygenated blood in reasonable amounts was being transferred to the systemic circuit. The main pulmonary arteries were not enlarged (4) Repeatedly in the clinical records, are notations indicating that the patient as a child was getting along very well although on exercise he became dyspneic and blue (5) the electrocardiogram done when the patient was 14 years old is the key item in the evidence pointing to a specific anatomic derangement (Fig 3) i e first, the evidence of right atrial enlargement, from the high potential of the P waves and second evidence of lack of right ventricular development revealed through absence of anterior and rightward QRS vectors (which features would be characteristic of right ventricular hypertrophy as expected in instances of pulmonary stenosis) It being characterized by a leftward vectorial shift of the QRS in the frontal plane and to the left and backward in the horizontal plane These electrocardiographic findings strongly point to obstruction at the tricuspid valve and a poorly developed right ventricular chamber



Fig 5 Exterior of heart viewed from the left. The transposed aorta (*A*) arises to the right and somewhat anterior to the pulmonary trunk (*P T*). The left (*L.A*) and right (*R A*) atrial appendages lie to the left of the great vessels, a condition termed left-sided juxtaposition of the atrial appendages.

septal defect occupied the wall of the infundibular region (Fig 8)

The left atrium showed slight thickening of its wall The mitral valve exhibited slight nodular fibrous thickening along the entire line of closure. The chordae and papillary muscles were normal.

The left ventricular wall was markedly hypertrophied measuring 1 9 cm in thickness. The left ventricular apex showed an area of thinning with a fibrous replacement indicative of a small healed transmural myocardial infarct The pulmonary trunk arose from the left ventricle Directly below the pulmonary valve, a fibrous ring narrowed the left ventricular outflow tract to a diameter of 11 mm. (Fig 10 *a*) The pulmonary valve, which was continuous with the mitral valve showed a dome shaped deformity resulting in a narrow orifice 8 mm in diameter (Fig 10 *b*) Brown granular vegetations were deposited on the ventricular aspect of the valve and upon the edges of the orifice. The pulmonary trunk was thin walled and exhibited a poststenotic dilatation.

The main pulmonary arterial branches were dilated and tortuous, and exhibited atrophy of the media. The pulmonary veins were not remarkable.



Fig. 6 *a*, Right atrium. The chamber is enlarged The wall is hypertrophied. An atrial septal defect (*A.D*) lies anterior to the ostium of the coronary sinus (*C.S.*). The tricuspid valve (*T V*) is hypoplastic. *b* Closeup view of tricuspid valve unopened and seen from above showing hypoplasia of the valve, thickening of the leaflets, and obstruction of the orifice by vegetative material (artifactual fragmentation of vegetative material)

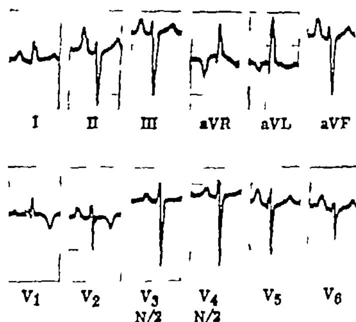


Fig. 4. Electrocardiogram at the age of 24 years.

ventricular chamber certainly was hypoplastic.

DR. MIRES J. BECKER: Let us now have a description of the pathologic findings.

DR. ANTON E. BECKER: The direct cause of death was extensive hemorrhage in the brain stem extending to the left side of the midbrain with rupture into the fourth ventricle and massive spread in the subarachnoid space. In addition multiple foci of old encephalomalacia were detected in the left basal ganglia and cerebellum. In the left frontoparietal region there was an area of collapsed cerebral tissue corresponding to the site of the previous (11 years) removal of the brain abscess.

The fundamental cardiac lesions were complete transposition of the great vessels, pulmonary and subpulmonary stenosis, congenital hypoplasia of the right ventricle and tricuspid valve, atrial and ventricular septal defects and closure of the tricuspid orifice by vegetations, the latter considered to be of bacterial origin. Postmortem blood culture was sterile.

The heart was enlarged weighing 530 grams. The great vessels were transposed with the aorta located anteriorly and slightly to the right of the pulmonary trunk. Each atrial appendage lay to the left of the great vessels, a condition termed left-sided juxtaposition of the atrial appendages (Fig. 5). The aortic arch was left sided with a normal branching pattern.

The right atrial chamber was slightly enlarged (Fig. 6 *a*). Its myocardium was hypertrophied. An atrial septal defect of the fossa ovalis type measuring 1 cm. in diameter was present.

The tricuspid valve was complex in appearance and of particular interest (Fig. 6 *b*). The orifice was basically narrow measuring 1.3 cm. in greatest diameter. The leaflets were small and thickened in a nodular fashion. The orifice was closed by firm gritty vegetative material which attached to the atrial surfaces of the leaflets (Figs. 6 *b* and 7).

Histologically the tricuspid leaflets were thickened by dense collagenous tissue. Deposited upon the atrial surfaces was vegetative material containing calcific foci. Some fibrous ingrowth into the vegetations had occurred and there was incomplete encapsulation of the vegetations by fibrous tissue. No residual bacteria were identified (Fig. 8).

The transposed aorta arose from the right ventricular chamber. The latter was relatively small (Figs. 7 and 9). It measured 5 cm. from the aortic valve to the apex of the chamber. The right ventricular wall was hypertrophied measuring 1.5 cm. in thickness. A large (2.0 cm.) ventricular

disease a cerebral abscess represents a constant threat. Usually there is no focus of infection within the heart. The possibility of a cerebral abscess complicating a right to-left shunt increases the longer the time that the patient is exposed to this possibility Thus, in the young this complication is relatively uncommon and the incidence rises as patients become older[8] It has been estimated that, in the natural



Fig. 9 Interior of hypoplastic right ventricle (*R.V.*) and aorta (*A.*) which arises from this ventricle. The wall of the right ventricle is hypertrophied The ventricular septal defect (*V.D.*) is also shown.



Fig. 10 Outflow tract of left ventricle (*L.V.*) A circular zone of fibrous tissue (*S.P.*) which attaches to the anterior mitral leaflet (*A.M.*) and the ventricular septum creates some pulmonary stenosis. Proximal to this lesion is the ventricular septal defect (*V.D.*) *b* Interior of pulmonary trunk (*P.T.*) and unopened pulmonary valve (*P.V.*) seen from above. The pulmonary valve shows a dome-shaped deformity and is stenotic. Vegetations are present on the edges of the valvular orifice.



Fig Sagittal section through the great vessel and the right side of the heart showing from the right atrium (*R A*) the atrial septal defect (*A.D*) The tricuspid valve is hypoplastic and the orifice is closed by vegetative material (*V*) The right ventricle (*R V*) is hypoplastic and the ventricular septal defect (*V.D*) is shown The transposed aorta (*A*) arises from the right ventricle The pulmonary trunk (*P T*) although appearing in the plane of section, arose from the left ventricle The stenotic pulmonary valve is also shown

Many small arteries, both systemic and pulmonary contained thrombi of varying ages. The majority of these were organized and recanalized No destructive lesions of the wall of arteries which contained thrombi were found

The kidneys were remarkable in showing signs of (1) glomerular enlargement and hypercellularity as often seen in cyanotic congenital heart disease[1] and (2) the malignant phase of hypertension as revealed by the fibrinoid change in the afferent arterioles and proximal glomerular capillaries.

DR MILES J BECKER Dr Edwards, will you make a closing discussion?

DR JESSE E. EDWARDS There are many facets to the case each of which is of considerable interest.

I would like to comment on three problems the cerebral manifestations, the basic anomaly and finally the peculiarities of the tricuspid valve

The cerebral manifestations are complex, starting with an abscess followed by seizures and finally by a hemorrhage. The seizures are considered to represent consequences of cerebral damage related to the cerebral abscess. When systemic venous blood bypasses the lungs as it does in the various types of cyanotic congenital heart

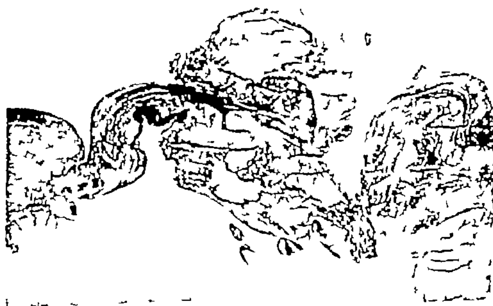


Fig 8 Low power photomicrograph of tricuspid valve. The valvular tissue is thickened by collagen. The atrial surface of the valve is covered by vegetative material which is in part, calcified and incompletely encapsulated by fibrous tissue. Plane of section lies to one side of the orifice so that the phenomenon of closure of the orifice by vegetative material is not illustrated (Elastic tissue stain. ×6)

lation and (2) in general causes of acquired complete obstruction of valvular orifices.

With regard to the effect upon the circulation closure of the tricuspid orifice by the vegetative process would have been responsible for an obligatory right-to-left shunt at the atrial level. Whereas, before closure of the tricuspid orifice only some of the blood returning to the right atrium would shunt across the atrial septum with closure all the returning blood would cross into the left atrium. Thus, while initially there was tricuspid stenosis (Fig 11 *a*) later there was in effect, tricuspid atresia (Fig 11 *b*).

While in the complex history of the patient there is no clear-cut illness that could be labeled as that of bacterial endocarditis, the nature of the acquired change in the tricuspid valve strongly favors bacterial endocarditis as the basis.

It is unusual that valves become completely closed as a result of acquired disease. In my experience the most common situation is for this to occur in a congenitally stenotic pulmonary valve, the result either of primary bacterial endocarditis of that valve or endocarditis secondary to primary involvement of the tricuspid valve.

Another basis occasionally seen in instances of the tetralogy of Fallot is progressive fibrosis of a stenotic pulmonary valve after creation of a systemic-pulmonary arterial anastomosis. Several years ago we noted closure by noninfected fibrous tissue of the principal orifice of the mitral valve in each of two cases with rheumatic mitral stenosis and a functioning commissurotomy. In those cases, closure of the mitral orifice may have resulted from embolism of left atrial thrombi to the mitral valve.

Final diagnosis

The final diagnosis is complete transposition with ventricular septal defect, pulmonary stenosis and hypoplasia of tricuspid valve and right ventricle. There is also secondary atresia of the tricuspid valve.

REFERENCES

1. Spear G. S.: Glomerular alterations in cyanotic congenital heart disease, Bull. Hopkins Hosp. 106:347 1960.
2. Maronde, R. F. Brain abscess and congenital heart disease Ann. Intern. Med. 33:602, 1950
3. Davachi, F. McLean, R. H. Moller J. H., and Edwards, J. E.. Hypoplasia of the right ventricle and tricuspid valve in siblings, J. Pediat. 71:869 1967
4. Sterns, L. P. Baker R. M. and Edwards, J. E. Complete transposition of the great vessels. Unusual longevity in case with subpulmonary stenosis, Circulation 29:610 1964.
5. Roberts, W. C., Friesinger G. C., Cohen, L. S., Mason, D. T. and Ross, R. S. Acquired pulmonic atresia. Total obstruction to right ventricular outflow after systemic to pulmonary arterial anastomosis for cyanotic congenital cardiac disease, Amer. J. Cardiol. 24:335, 1969
6. Bonnabeau, R. C., J. Stevenson, J. E., and Edwards, J. E.: Obliteration of the principal orifice of the stenotic mitral valve. A rare form of restenosis, J. Thorac. Cardiovasc. Surg. 49:264 1965

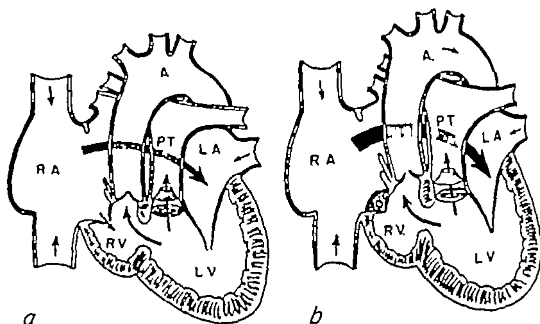


Fig 11 Diagrammatic portrayal of the anomalies and of the resulting central circulation a The basic situation b After closure of tricuspid valve by vegetations.

history of patients with cyanotic congenital heart disease about 10 per cent develop the complication of cerebral abscess In the patient under discussion this complication developed when he was 13 years old

The terminal cerebral hemorrhage does not appear to be related to the cerebral abscess which had been treated about 11 years prior to death While the basis for the fatal cerebral hemorrhage is not determined the possibility of a mycotic aneurysm secondary to bacterial endocarditis of the tricuspid valve must be entertained Another possibility is that this was a complication of the existing hypertension

The basic anomaly in the case presented was complete transposition of the great vessels associated with a ventricular septal defect hypoplasia of the right ventricle and tricuspid valve and pulmonary and subpulmonary stenosis. The associated malformations may have had a beneficial effect upon the circulation in complete transposition and may account for the unusually long life for a patient with this condition

Isolated hypoplasia of the right ventricle and of the tricuspid valve is a condition with a tendency for familial occurrence and is usually associated with an otherwise normal heart [3] The restrictive effects of the narrow tricuspid valve and small right ventricle favor a right to-left shunt at the atrial level In otherwise normal hearts, the right to left shunt is a major problem When complete transposition is associated the right to-left transatrial shunt may be advantageous in that it aids in intracardiac mixing of blood

Another advantage in the case under consideration is that there was stenosis in the pathway between the left ventricle and the pulmonary arterial systems in the forms of subpulmonary and pulmonary valvular stenosis (Fig. 11 a) Obstruction to pulmonary flow in the presence of a ventricular septal defect is a favorable combination in complete transposition as oxygenated blood is directed to the right ventricle and the aorta [4]

The tricuspid valve was of particular interest In addition to congenital hypoplasia vegetations, which were consistent with bacteriologically healed bacterial endocarditis, were found to close the tricuspid orifice.

The electrocardiographic picture showed evidence for a change in the character of the right atrium The probability is that this resulted from the closure of the tricuspid orifice with the vegetations later to be found at necropsy

Two aspects of the vegetative process involving the tricuspid valve warrant discussion namely (1) the effect upon the circu

hypertension including systolic hypertension. There were 95 men and 24 women. Average ages of the groups with sustained hypertension, labile hypertension and systolic hypertension were 37.5, 23.1 and 21.4 years old, respectively.

Patients with chronic glomerulonephritis or diabetes mellitus, whose hypertension was not thought to be secondary to chronic glomerulonephritis or diabetes mellitus but primary with coincidental diseases, were classified as essential hypertensive with chronic glomerulonephritis or diabetes mellitus.

Renal arteriography was performed by the translumbar method in 21 cases, by transfemoral aortography in 174 cases, and selective renal arteriography in 16 cases. Films were usually taken 2 or 3 per second from the beginning of the injection of contrast medium to 10 seconds. The following parameters were analyzed: renal vascular pattern, the appearance and disappearance time of arborization and the beginning of the nephrogram in both kidneys according to Hotovy and co-workers, renal length by nephrogram and renal index and renal difference index also by nephrogram according to Friedenberg and co-workers.

The intravenous pyelogram was obtained by conventional methods, and by rapid sequence urography and urea wash out urography according to Amplatz. Renograms were done with ^{131}I Hippuran.

Peripheral venous blood was drawn in the recumbent position for the measurement of renin activity. Renal venous blood was sampled in the recumbent position by transfemoral catheterization using the Seldinger technique for the measurement of individual renal venous renin activity while patients received a 250 mEq sodium diet. Plasma renin activity was measured by Skinner's improved method.[14]

Results

Two or more arteries springing from the aorta or the iliac artery and distributed to the kidney were defined as multiple renal arteries according to Boijsen.[11] This does not include prehilar branches from a main renal artery. The branch arteries which occurred within the first centimeter of the main renal artery were called "early branching" according to Robertson and associates. In those patients who had multiple renal arteries with early branching only multiple renal arteries were counted.

There was no significant difference in the incidence of multiple renal arteries revealed by three different techniques of renal arteriography, namely, 23.8 per cent by translumbar aortography, 28.7 per cent by transfemoral aortography, and 25.0 per cent by selective renal arteriography (chi-square test, $p > 0.5$).

The incidence of multiple renal arteries in patients with various diseases is summarized in Table I. Although multiple renal arteries were more often found in essential hypertensive than normotensive patients, there was no statistical significance (chi-square test, $0.3 > p > 0.2$). There was no significant difference in the incidence of multiple renal arteries in essential hypertensive patients according to age. Moreover, there was no significant difference in the incidence of multiple renal arteries among sustained, labile, and systolic hypertensive patients, namely, 31 of 96 cases (32.3 per cent), 3 of 12 cases (25.0 per cent), and 3 out of 11 cases (27.3 per cent), respectively (chi-square test, $p > 0.5$).

Renal function in essential hypertension was studied by intravenous pyelogram, renogram, and angiogram. Such comparisons as shown in Table II were made between essential hypertensive patients with single renal artery and with multiple renal arteries. No statistically significant difference was found in any of these comparisons, suggesting that multiple renal arteries could not be correlated with a specific defect.

Plasma renin activity of patients with essential hypertension is shown in Tables III and IV. The mean value of plasma renin activity from the peripheral vein obtained from 25 healthy subjects while on a 250 mEq sodium diet was 1.4 ± 0.2 ng per milliliter per hour (95 per cent confidence limit) and 1.4 ± 1.1 ng per milliliter per hour (5 per cent rejection limit).[15] Four of 20 patients with essential hyper-

Essential hypertension and multiple renal arteries

Gakuji Nomura, M.D.
Masao Kurosaki, M.D.
Toshihiko Kondo, M.D.
Jugoro Takeuchi, M.D.
Kanazawa, Japan

In 1951 Marshall[1] reported a frequent association between multiple renal arteries and hypertension in autopsied cases. Subsequently, Robertson and associates[2,3] and Davis and co-workers[4] asserted a frequent association of multiple renal arteries and hypertension by angiographic study.

On the other hand, Brown and colleagues[5] and Davies and Sutton[6] reported that there was no significant difference in the incidence of multiple renal arteries in normotensive and in hypertensive subjects based on angiographic study.

In view of these conflicting opinions, we studied the incidence of multiple renal arteries in essential hypertension and compared renal function and plasma renin activity in hypertensive patients with multiple renal arteries and those with single renal arteries.

Material and methods

Two hundred forty-three consecutive renal arteriograms from a variety of patients obtained during the past six years at the First Department of Internal Medicine, Kanazawa University Hospital, were studied. Thirty-two cases were excluded from this series because of inadequate visualization.

Blood pressures of 140/90 mm. Hg or over in patients younger than 35 years old and 150/90 mm. Hg or over in patients older than 35 years were considered to be hypertensive. Possible etiologies of hypertension were looked for by urinalysis and culture, serum electrolytes, thyroid function tests, urinary catecholamine excretion, plasma renin activity, intravenous pyelography, renogram, renal scan, renal biopsy in some cases, and angiography as well as history and physical findings. Hospitalized patients who consistently showed blood pressures higher than the normal range without antihypertensive drugs during at least three days of observation were classified as sustained hypertensive. Patients who were hypertensive on admission but showed at least one casual blood pressure reading in the normal range during the first three days, were classified as labile hypertensive. Relatively younger patients who showed systolic hypertension and no evidence of cardiovascular disease, endocrine disorder, and so on were classified as systolic hypertensive. One hundred and nineteen cases were diagnosed as essential

From the First Department of Internal Medicine, School of Medicine, Kanazawa University, Kanazawa, Japan.
Reprint requests to: Jugoro Takeuchi, M.D., First Department of Internal Medicine, School of Medicine, Kanazawa University, Kanazawa, Japan.

Table III Renin activity in essential hypertensive patients with single renal artery

Patient	Age	Sex	Blood pressure (mm. Hg)	Fundi*	Peripheral vein		Renal vein		
					250 mEq.	30 mEq	Left	Right	Left/right
2 870	16	M	176/90		1 5				
2 963	22	F	184/108	0	1 3	4 9			
3 065	18	M	178/86	I	1 0				
3 101	60	M	160/94	II	2 9	4 1			
3 147	31	M	170/100	II	1 9	3 6			
3 172	24	F	160/102	II	0 8	2 8			
3 177	34	M	160/90	I	1 1	3 1	4 1	2 0	2 1
3 253	36	M	220/130	I	0 5	1 3			
3 289	29	M	160/100	0	1 5	5 2	1 1	0 9	1 2
3 308	32	M	180/110	I	1 8	3 7			
3 413	21	M	190/90		2 0	8 3	3 4	3 2	1 1
3 514	35	F	160/100	0	2 1	3 4			
3 994	16	M	150/90	0	1 8			2 3	
4 024	52	M	180/100	II	1 9		1 3	0 9	1 4
4 039	64	M	180/110	III	8 8		6 3	6 5	1 0
4 036	41	M	186/120	I	4 7		4 4	4 7	0 9
3 109	25	M	132/98		5 8				
3 948	40	F	170/126	I	1 0		0 9	1 0	0 9
4 120	60	M	170/92	II	1 3		0 8	0 8	1 0
3 995	43	M	182/122	I	1 5		0 8	0 7	1 1
					2.0 ± 0 8†	4.2 ± 1.3†	2.6 ± 1.6†	2.6 ± 1.5†	1.2 ± 0.3†

*Keith-Wagener classification.
†Mean ± 95 per cent confidence limit.

Table IV Renin activity in essential hypertension with multiple renal arteries

Patient	Age	Sex	Blood pressure (mm. Hg)	Fundi	MRA	Peripheral vein		Renal vein		
						250 mEq	30 mEq	Left	Right	Left/right
2 805	21	M	164/122	0	R	2 4				
3 018	43	M	230/120	III	R	1 0		1 5	1 0	1 5
3 125	52	F	200/120	II	R	0 9	3 1			
3 226	39	M	180/130	II	R	1 4		2 6	2 8	0 9
3 305	34	M	170/100		R	1 9	3 8	3 4	4 0	0 9
3 331	35	F	200/100	I	L	1 8	2 9	1 8	1 8	1 0
3 501	28	F	172/108	0	L	1 6	2 2			
4 004	47	M	180/110	I	L	0 6		0 9	0 8	1 1
4 056	40	M	162/100	III	R	1 0		1 5	1 7	0 9
4 174	36	M	150/118	I	L	2 5		2 6	2 4	1 1
2 970	64	M	200/100	II	B	1 0				
3 946	20	M	164/84		B	1 7	4 1			
4 070	50	M	150/96	I	B	0 0		0 7	0 5	1 4
4 090	28	M	150/100	0	B	0 6		0 8	0 8	1 0
4 192	27	M	160/120	II	L	1 0		1 3	1 3	1 0
						1.3 ± 0 4†	3.7 ± 1.4†	1 7 ± 0.8†	1.7 ± 0 8†	1 0 ± 1.1†

MRA = Multiple renal arteries, R, right side L, left side; B, both sides.
[illegible] fication.
[illegible] confidence limit.

Table I The incidence of multiple renal arteries and early branching

Diagnosis	Multiple renal arteries	Early branching	Total
Essential hypertension	37/119 (31 1%)	8/119 (6 7%)	45/119 (37 8%)
Essential hypertension with glomerulonephritis or diabetes mellitus	4/14 (28 6%)	0/14 (0 0%)	4/14 (28 6%)
Secondary hypertension	9/37 (24 3%)	0/37 (0 0)	9/37 (24.3%)
Normotensive	9/41 (22 0%)	3/41 (7 3%)	12/41 (33 2%)
Total	59/211 (28 0%)	11/211 (5 2%)	70/211 (33 2%)

Table II Renal function in essential hypertension

Parameters	Essential hypertension with single renal artery	Essential hypertension with multiple renal arteries	Chi square test
IVP Difference of			
(1) pyelocalyceal appearance (rapid sequence urogram)	4/ 0 (20 0%)	1/18 (5 5%)	0 2 > p > 0 1
(2) pyelocalyceal concentration	4/65 (6 2%)	1/31 (3 2%)	p > 0 5
(3) calyceal washout (urea infusion urogram)	1/5 (20 0%)	0/4 (0 0%)	0 5 > p > 0 3
Renogram Abnormal L/R ratio of			
(1) time to peak amplitude (0 8 < L R < 1 2)	4/39 (10 3)%	2/18 (11 1%)	p > 0 5
(2) time to 75% amplitude (0 7 < L/L < 1 3)	4/39 (10 3%)	3/18 (16 7%)	0 5 > p > 0 3
(3) peak amplitude (0 7 < L/R < 1 3)	8/39 (20 5 %)	3/18 (16 7%)	p > 0 5
(4) angle of segment B (0 9 < L/R < 1 5)	14/39 (35 9%)	4/18 (22 2%)	0 5 > p > 0 3
(5) ratio of peak amplitude to 15 min amplitude (0 8 < L/R < 1)	1/39 (2 5%)	1/18 (5 6%)	p > 0 5
Angiogram Difference of			
(1) appearance of arborization	4/56 (7 1%)	4/30 (13 3%)	0 5 > p > 0 3
(2) disappearance of arborization	5/56 (8 9%)	6/30 (20 0%)	0 5 > p > 0 3
(3) beginning of nephrogram	8/56 (14 3%)	5/30 (16 7%)	p > 0 5
(4) renal length ≥ 1 5 cm	9/60 (15 0%)	3/29 (10 3%)	p > 0 5
(5) renal difference index > 8 8	13/60 (21 7)	4/29 (13 8 %)	0 5 > p > 0 3

*IVRBF 5 per cent rejection limit of 15 cases of essential hypertension with single renal artery whose renal plasma flow was more than 400 ml. per minute

tension with single renal artery showed increased peripheral venous renin activity Patients 4 039 and 4 036 showed marked arterio- and arteriolosclerosis by renal biopsy which might be relevant to abnormal increase of renin activity In two other cases renal biopsy was not done and a cause of abnormal increase of renin activity was not clear On the other hand none of 15 patients with essential hypertension with multiple renal arteries showed any increase in peripheral venous renin activity However there was no significant difference in the mean value of peripheral venous renin activity between these groups (t test p > 0 05) No patient in either group except No 3 413 showed the increase in peripheral venous renin activity to such degree as usually seen in renovascular hypertension after sodium restriction of 30 mEq daily

A difference in renin activity from one

*Table V. The incidence of renal anomalies**

Renal artery	*Essential hypertension*	*Others*	*Total*
Single	7/83 (8.4%)	3/68 (4.4%)	10/151 (6.6%)
Multiple	2/36 (5.5%)	2/24 (8.3%)	4/60 (6.7%)
Total	9/119 (7.6%)	5/92 (5.4%)	14/211 (6.6%)

*Renal aplasia and hypoplasia, double pelvis, and double ureter were included in this category

content. We suggest that there is no ischemic area which is significant enough to be an etiological factor of hypertension in the kidney with multiple renal arteries at least in terms of renin activity.

Recently Ashken[13] and Ashken and Chapman,[14] using the combination of microangiography and histology, reported that there was no evidence of different vascularity in the renal segments supplied by the separate artery compared to the rest of the kidney and no evidence of interzonal ischemia. Our results with plasma renin activity are consistent with this.

In essential hypertension, renal anomaly or dysplasia was observed in only a small percentage of patients, and it was rather frequently seen in single renal artery than in multiple renal arteries. This suggests that the general cause of hypertension observed in multiple renal arteries cannot be related to renal anomaly or dysplasia itself (Table V).

Summary

Two hundred forty-three consecutive renal arteriograms were studied. Thirty-seven of 110 cases of essential hypertension (31 per cent) and 9 of 41 normotensive cases (22 per cent) revealed multiple renal arteries, showing that there is no significant difference in the incidence of multiple renal arteries between the two groups.

Renal function study by intravenous pyelography, renogram, and angiography showed no difference between essential hypertension with multiple renal arteries and that with single renal artery. Plasma renin activity in peripheral and renal venous blood also showed neither increase nor difference in both kidneys, suggesting no significant ischemic changes in the kidney with multiple renal arteries. The general cause of hypertension observed in multiple renal arteries also cannot be related to renal anomaly or dysplasia itself.

We conclude that multiple renal arteries are not an etiological factor in essential hypertension.

REFERENCES

1. Marshall, A. G.: Aberrant renal arteries and hypertension, Lancet 2:701, 1951.
2. Robertson, P. W., Klidjian, A., Hull, D. H., Hilton, D. D., and Dyson, M. L.: The assessment and treatment of hypertension, Lancet 2:567, 1962.
3. Robertson, P. W., Hull, D. H., Klidjian, A., and Dyson, M. L.: Renal artery anomalies and hypertension, Amer. Heart J. 73:296, 1967.
4. Davis, G. D., Kincaid, O. W., and Hunt, J. C.: Roentgenologic evaluation of multiple renal arteries, Amer. J. Roentgenol. 90:583, 1963.
5. Brown, J. J., Owen, K., Peart, W. S., Robertson, J. I. S., and Sutton, D.: The assessment and treatment of hypertension, Lancet 2:832, 1962.
6. Davies, E. R., and Sutton, D.: Hypertension and multiple renal arteries, Lancet 1:341, 1965.
7. Hotovy, E., Losonci, A., and Lakos, J.: Serial nephrography in hypertension, Acta Radiol. 7:177, 1968.
8. Friedenberg, M. J., Walz, B. J., McAlister, W. H., Locksmith, J. P., and Gallagher, T. L.: Roentgen size of normal kidneys, Radiology 84:1022, 1965.
9. Amplatz, K.: Two radiographic tests for assessment of renovascular hypertension, Radiology 79:807, 1962.
10. Skinner, S. L.: Improved assay methods for renin "concentration" and "activity" in human plasma, Circ. Res. 20:391, 1967.
11. Boijsen, E.: Angiographic studies of the anatomy of single and multiple renal arteries, Acta Radiol. (Suppl.) 183, 1959.
12. Kuroseki, M.: Studies on the renin-angiotensin

kidney to the other was not observed except one case with single renal artery

The incidence of congenital renal anomalies observed in this series such as renal aplasia hypoplasia double pelvis or double ureter is shown in Table V Renal anomalies were observed slightly more often in essential hypertension than in other diseases. Hydronephrosis or horseshoe kidney was not included in our study

Discussion

Marshall[1] originally reported the association of multiple renal arteries and hypertension from the results obtained in autopsy cases. Since then conflicting results have been obtained by anatomical and angiographic study Robertson and associates[2,3] asserted a frequent association of multiple renal arteries and hypertension from their angiographic study Davis and colleagues[4] also supported this concept On the other hand Brown and co-workers[5] and Davies and Sutton[6] challenged the unusually high incidence of multiple renal arteries reported by Robertson and associates

The incidence of multiple renal arteries in our series was not significantly different between patients with essential hypertension and normotensive subjects There was no difference in the incidence even if early branching was added to multiple renal arteries (Table I) Our series included more patients in the younger age group This might distort the incidence of multiple renal arteries in the general population with essential hypertension i e it might be higher in younger hypertensive patients. However there was no significant difference in the incidence in patients with essential hypertension according to age in our series. Davies and Sutton also pointed out that age did not affect the incidence We cannot explain the difference between our results and those of Robertson and associates[3] except race and patient selection The criterion of hypertension used by Robertson and associates was 150/100 mm Hg or over However the almost equal incidence of multiple renal arteries among sustained labile, and systolic hypertensive patients in this study suggests that it is not affected by severity of hypertension

It has been supposed by some investigators that there might be renal circulatory disturbance with multiple renal arteries, and this might be a cause of hypertension. In this regard we studied the renal function in essential hypertension with multiple renal arteries compared with essential hypertension with a single renal artery by intravenous pyelography renogram, and angiography

Functional differences in one kidney compared to the other as revealed by intravenous pyelogram and renogram were similar in patients with multiple renal arteries and with single renal artery Differences in renal size and in angiographically studied renal functions were not affected by the presence or absence of multiple renal arteries (Table II) From these results we can conclude that there is no important circulatory disturbance associated with multiple renal arteries. Hunt and colleagues[12] reported that in separate renal function studies of 36 cases of essential hypertension the differences between the kidneys of patients with aberrant arteries were minimal From this report as well as our results it may be said that renal circulatory changes in multiple renal arteries if any are not likely to be a cause of hypertension

Robertson and associates[3] suggested that in multiple renal arteries some segments of the kidney might be hypovascular It is also supposed that multiple renal arteries may be associated with renal anomaly or dysplasia which might itself contribute to hypertension In these cases, we may be able to obtain some clue as to the relationship between hypertension and multiple renal arteries by assessment of plasma renin activity or pressor substances and also by assessment of the incidence of congenital renal malformations with multiple renal arteries in patients with hypertension.

Our results did not show any abnormality in renin activity of peripheral or renal venous blood in essential hypertension with multiple renal arteries (Tables III and IV) Since the renal vein consistently shows large and numerous intrarenal venovenous communication blood sampling from one renal vein even in the case associated with multiple renal veins might not miss other veins with a high renin

*Table V. The incidence of renal anomalies**

Renal artery	Essential hypertension	Others	Total
Single	7/83 (8 4%)	3/68 (4 4%)	10/151 (6 6%)
Multiple	2/36 (5 5%)	2/24 (8 3%)	4/60 (6 7%)
Total	9/119 (7 6%)	5/92 (5 4%)	14/211 (6 6%)

*Renal ectopia and hypoplasia, double pelvis, and double ureter were included in this category.

content. We suggest that there is no ischemic area which is significant enough to be an etiological factor of hypertension in the kidney with multiple renal arteries at least in terms of renin activity

Recently Ashken[13] and Ashken and Chapman,[14] using the combination of microangiography and histology reported that there was no evidence of different vascularity in the renal segments supplied by the separate artery compared to the rest of the kidney and no evidence of interzonal ischemia. Our results with plasma renin activity are consistent with this.

In essential hypertension, renal anomaly or dysplasia was observed in only a small percentage of patients, and it was rather frequently seen in single renal artery than in multiple renal arteries. This suggests that the general cause of hypertension observed in multiple renal arteries cannot be related to renal anomaly or dysplasia itself (Table V)

Summary

Two hundred forty-three consecutive renal arteriograms were studied. Thirty seven of 110 cases of essential hypertension (31 per cent) and 9 of 41 normotensive cases (22 per cent) revealed multiple renal arteries, showing that there is no significant difference in the incidence of multiple renal arteries between the two groups.

Renal function study by intravenous pyelography renogram and angiography showed no difference between essential hypertension with multiple renal arteries and that with single renal artery. Plasma renin activity in peripheral and renal venous blood also showed neither increase nor difference in both kidneys, suggesting no significant ischemic changes in the kidney with multiple renal arteries. The general cause of hypertension observed in multiple renal arteries also cannot be related to renal anomaly or dysplasia itself.

We conclude that multiple renal arteries are not an etiological factor in essential hypertension

REFERENCES

1. Marshall, A. G. Aberrant renal arteries and hypertension, Lancet 2 701 1951.
2. Robertson, P W Klidjian, A., Hall, D H., Hilton, D D., and Dyson, M. L.: The assessment and treatment of hypertension, Lancet 2:567 1962.
3. Robertson, P W Hall, D H., Klidjian, A., and Dyson, M L. Renal artery anomalies and hypertension, Amer. Heart J 73:296, 1967
4. Davis, G. D Kincaid, O. W and Hunt, J C. Roentgenologic evaluation of multiple renal arteries, Amer J Roentgenol. 90:583 1963.
5. Brown, J J Owen, K., Peart, W S., Robertson, J I. S., and Sutton, D.: The assessment and treatment of hypertension, Lancet 2:832, 1962.
6. Davies, E. R., and Sutton, D. Hypertension and multiple renal arteries, Lancet 1:341 1965.
7. Hotovy E., Losonci, A., and Lakos, J.: Serial nephrography in hypertension, Acta Radiol. 7 177 1968.
8. Friedenberg, M. J Walz, B. J McAlister W H., Locksmith, J P and Gallagher T L.: Roentgen size of normal kidneys, Radiology 84 1022, 1965.
9. Amplatz, K.: Two radiographic tests for assessment of renovascular hypertension, Radiology 79:807 1962.
10. Skinner S. L.: Improved assay methods for renin concentration and activity" in human plasma, Circ. Res. 20:391 1967
11. Boijsen, E.: Angiographic studies of the anatomy of single and multiple renal arteries, Acta Radiol. (Suppl.):183 1959
12. Kuroaki, M.: Studies on the renin-angiotensin

system I Plasma renin activity in various types of hypertension Jap J Nephrol. 11:681 1969

13 Hunt J C, Maher F T Green L F and Sheps, S G Functional characteristics of the separate kidneys in hypertensive man Amer J Cardiol. 17:498 1966

14 Smith G T Calne R Y Murray J E and Dammin G J Anatomic observations on the renal vessels in man with reference to kidney transplantation, Surg Gynec. Obstet. 115:61, 1962

15. Ashken, M H A study of the renal vascular patterns in hypertension, chronic pyelonephritis and other diseases, Ann. Roy Coll. Surg Eng 40:82 1967

16. Ashken, M H and Chapman M A study of the renal vascular patterns in hypertension and chronic pyelonephritis, J Urol. 101:661 1969

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff Alan F Lyon, and Julian Frieden

Current status of diastolic augmentation for circulatory support*

Leslie A Kuhn, M.D
New York N Y

One of the problems in treating acute myocardial infarction with shock with available pharmacologic agents has been that measures to increase the diminished *coronary flow* to the acutely ischemic myocardium by raising coronary perfusion (aortic) pressure are associated with increments of myocardial oxygen requirement. A variety of techniques have been devised with the attractive rationale of increasing coronary blood flow by increasing aortic pressure in diastole (at the phase of maximum coronary flow) and diminishing aortic pressure in systole thereby lessening the pressure work and the oxygen requirement of the left ventricle. The methods used have been given numerous designations, including *counterpulsation* diastolic augmentation postsystolic myocardial augmentation, and phase shift pumping. In this brief review we will assess the experimental evidence which has accumulated concerning the hemodynamic and cardiac metabolic effects of these methods, their present status in regard to clinical application and their prospects for future use. The requested *format* of these articles is such that it will not be possible to credit each of the *many* investigators in these areas with his unique contribution or to annotate each of the statements made with its appropriate reference but a few selected references are appended at the conclusion of the article.

Experimental results

Counterpulsation of blood. In 1953 Kantrowitz and Kantrowitz demonstrated that the total coronary flow of dogs could be augmented by increasing aortic pressure during diastole by mechanical retardation of the aortic pulse. There have been several devices employed since, which counterpulsate aortic blood by pumping it in diastole and withdrawing it from the arterial circulation in systole thus altering the form of the aortic pressure pulse. This was accomplished initially through one or two catheters inserted into the femoral arteries, the pump being triggered by the R wave of the electrocardiogram. Various alterations of this technique to produce the same physiologic effects have been reported, among them utilization of the systolic pressure wave of the arterial pulse rather than the electrocardiogram, avoiding some of the problems caused by arrhythmias, utilization of external pulsed pressure with a leg pressure unit, theoretically avoiding the necessity for arterial cannulation and utilization of synchronized venoarterial shunting which may provide greater stroke volume than that

From the Division of Cardiology Department of Medicine, Mount Sinai School of Medicine, New York, N. Y
*Opinions expressed are based on research supported by Research Grant HE 04133, National Heart Institute, United States Public Health Service

obtained with arterioarterial pumping The use of an aortic balloon inflated in diastole and deflated in systole has evoked widespread interest and will be discussed subsequently

The precise physiologic effects of counterpulsation of blood are still in some dispute despite theoretic considerations which would indicate that it is a rational technique Radiographically the coronary tree has shown increased anastomoses following the use of blood counterpulsation in experimental plastic sphere coronary embolization Although there have been some reports of increased coronary flow with this technique when used in experimental shock produced by hemorrhage or myocardial infarction other investigators have shown little increment of coronary flow with counterpulsation during profound hypotension probably owing to readjustment of peripheral coronary vascular resistance or failure of the apparatus to augment coronary perfusion pressure sufficiently to increase flow Increased survival following experimental coronary occlusion has been reported as has expected reduction of myocardial oxygen consumption and left ventricular pressure work in the normal dog However reduction of cardiac output has also been noted as well as decrease in central venous oxygen saturation In other investigations there has been no reduction of myocardial oxygen consumption despite reduction of the time-tension index (the area under the systolic arterial pressure curve)

There is good evidence that the hemodynamic effects of counterpulsation of blood may vary with the level of arterial pressure normal systolic arterial pressure being reduced to considerably greater extent than an initially depressed systolic pressure Our own investigations have indicated the importance of an adequate level of aortic pressure as a determinant of the efficacy of counterpulsation When counterpulsation of blood was performed even in the central aorta during profound hypotension there was only slight and inconsistent improvement of the hemodynamic abnormalities and anaerobic myocardial metabolic changes associated with acute myocardial infarction with shock. However when during central aortic counterpulsation an adequate central aortic (coronary perfusion) pressure was obtained mechanically in myocardial infarction with shock by means of circulatory compartmentalization achieved by phased or nonphased balloon obstruction of the lower abdominal aorta anaerobic myocardial metabolic alterations were reversed and there were substantial elevations of cardiac output coronary perfusion pressure, and coronary flow Because of the simultaneous effects of counterpulsation these results were achieved with only slight increment of myocardial oxygen consumption. On the basis of these experimental considerations, we feel that counterpulsation of blood alone even though it may reduce somewhat myocardial oxygen requirement is unlikely to be of sufficient aid in the circumstance in which it is most needed, profound hypotension following acute myocardial infarction probably because it fails to increase adequately coronary perfusion pressure and flow Alternative means of increasing coronary perfusion pressure and flow enhance the effects of counterpulsation of blood

Balloon aortic counterpulsation Originally introduced by Moulopoulos and subsequently investigated by Clauss and associates and Kantrowitz and associates, as well as other groups, this technique was devised to achieve the same physiologic effects as counterpulsation of blood Since it employs a polyurethane balloon inflated rapidly by a gas (usually helium) and positioned just distal to the carotid artery balloon counterpulsation has the advantage of much less trauma to the blood elements as compared to blood counterpulsation In addition because the balloon may be inserted on a relatively small cardiac catheter it is associated with easier peripheral arterial cannulation than is blood counterpulsation The latter generally requires cannulation of both femoral arteries or the lower abdominal aorta with large-bore catheters in order to pump sufficient volumes of blood to effect significant alterations of the aortic pressure pulse

Intra aortic balloon pumping was introduced as a means of reducing left ventricu

lar work. Although experimental results with balloon aortic pumping have shown many of the same effects as blood counterpulsation, i.e. reduction of left ventricular oxygen consumption variable increments of coronary flow and improvement of mortality in experimental myocardial infarction it is probable that much of its efficacy rests on other principles since central aortic counterpulsation of blood alone may affect insufficient changes of aortic pressure to produce substantial increment of coronary flow and cardiac output or alteration of anaerobic myocardial metabolism when used during significant hypotension Our own investigations have indicated that when there is advanced hypotension following acute myocardial infarction counterpulsation produced by phasic inflation and deflation of a balloon in the upper thoracic aorta is more effective in reversing the hemodynamic and metabolic abnormalities of cardiogenic shock than central aortic counterpulsation of blood alone. A greater increment of coronary perfusion pressure and flow is produced by balloon inflation. We attribute this in part to circulatory compartmentalization produced by balloon aortic obstruction even though the balloon may not be fully occlusive, as well as to the pumping action of the inflated balloon itself In extreme hypotension even balloon aortic counterpulsation may be ineffective in relieving the observed hemodynamic and cardiac abnormalities. In such instances beneficial effects may be obtained by further circulatory compartmentalization achieved by inflation of an additional balloon distal to the main pumping balloon or by placement of a distal valve restricting cardiac stroke ejection to the proximal aortic segment. These experimental results indicate that mere reduction of left ventricular work by counterpulsation is an insufficient principle upon which to base therapy in situations with advanced hypotension and that the beneficial results of the technique are more probably attributable to its efficacy in raising the diminished coronary perfusion pressure and flow This is accomplished more effectively with phasic balloon obstruction of the aorta than with counterpulsation of blood alone. We have also obtained such beneficial effects (increasing cardiac output aortic pressure and coronary flow and reversing anaerobic myocardial metabolic alterations in acute myocardial infarction with shock) with nonphased balloon obstruction of the lower abdominal aorta although phased aortic obstruction appears more rational and desirable, particularly in protecting the tissues supplied by the distal aorta from ischemia. The results suggest that in treating profound hypotension in acute myocardial infarction with shock, prime consideration be given to improving aortic perfusion pressure and hence the diminished coronary flow rather than to reduction of left ventricular work and oxygen requirement, although of course this would be desirable if adequate coronary flow could be obtained simultaneously Mechanical or pharmacologic techniques which result merely in reduced oxygen consumption without providing increased aortic pressure and coronary flow in the presence of profound hypotension in acute myocardial infarction most often fail to alter consistently favorably the low cardiac output and anaerobic cardiac metabolic derangements of the shock state. Counterpulsation of peripheral blood unless combined with other techniques to raise the central aortic perfusing pressure and volume (such as venoarterial shunting or a phased or nonphased distal aortic balloon) is generally within this category of devices, particularly when used during marked hypotension. In our experience this applies also to central aortic counterpulsation of blood but a recent report indicates considerable hemodynamic and metabolic improvement with counterpulsation of a small volume of blood in the central aorta in a small number of animals with acute myocardial infarction and shock.

Clinical results

Counterpulsation of blood Clinical experience with this technique has been very limited a somewhat larger number of patients have been studied with balloon aortic counterpulsation. Rosensweig and associates report nine patients with acute myocardial infarction with shock (systolic

pressure 80 mm Hg or below with clinical signs of shock) Four of these patients have survived after just one hour of counterpulsation via a common femoral artery In six of the patients who had had no circulatory arrest long term survival was obtained in four However they were under 60 years of age were lucid at the time treatment was instituted and were treated early in the shock state Obviously these were patients who were better risks to begin with Therefore the natural course of their disease with appropriate medication without circulatory assistance cannot be compared to the other patients who did not respond to counterpulsation It seems difficult to conceive of one hour of counterpulsation affecting a permanent cure of prolonged refractory shock following acute myocardial infarction even though increased coronary collaterals may be opened during that period particularly when successful application of balloon counterpulsation has required many hours of pumping The conclusions concerning the efficacy of the technique are also vitiated by the lack of published detailed hemodynamic alterations in these patients including cardiac output and aortic and left ventricular pressures. Of seven patients with acute myocardial infarction and shock similarly treated by Soroff and associates one long term survivor was reported

Additional clinical experience with counterpulsation of blood has been reported by Jacobey and associates All four treated patients with myocardial infarction and shock died but they had prolonged shock prior to treatment An interesting group of patients with severe angina pectoris with three-vessel coronary disease was also treated with one and one half to two hours of counterpulsation Of seven patients so treated three improved substantially with concomitant filling of coronary vessels which did not fill with contrast media prior to therapy The value of such therapy in severe angina pectoris has not been established and it is unlikely that it will offer a unique and significant therapeutic advantage in this disease Intensive medical therapy (including propranolol) myocardial revascularization or direct surgical approach to the coronary vessels, including saphenous vein bypasses, appear more rational and are certainly better established procedures at this time.

Balloon counterpulsation. Clinical trials of balloon counterpulsation have also been very limited However the technique is somewhat easier to apply than is that requiring counterpulsation of blood and has had more frequent use. The largest series reported is that of Kantrowitz and associates, comprising about 30 patients. Smaller numbers of patients have been studied by Buckley and associates and by Summers and associates. In addition, several groups have studied occasional patients with this technique but have not reported detailed findings.

The results are difficult to evaluate because detailed hemodynamic studies prior to during and after circulatory support with this technique are not available in appreciable numbers of patients. There has been no randomization of patient selection but pump support has been applied to those patients with cardiogenic shock who were apparently refractory to available medical therapy undoubtedly a high risk group. Kantrowitz and associates divided their patients, for purposes of analysis, into two groups one having early circulatory failure within 36 hours of the onset of myocardial infarction and the other delayed circulatory failure occurring later than 36 hours after the onset of infarction Of 21 patients analyzed in detail with circulatory assistance periods ranging from one and one half to 55 hours (average 19 hours) 7 survived to be discharged from the hospital of whom 5 were alive and well from eight and one half to 13 months following the onset of myocardial infarction All patients in the delayed failure group died as did 9 of 16 patients in the early failure group However it is reported that the shock syndrome was reversed at least temporarily in 15 of 16 patients in the latter group There were 3 deaths attributed to procedural causes, 2 during interruption of pumping and one (in which there was not acute myocardial infarction) attributed to ventricular fibrillation related to a pacemaker signal Of concern also was a rather high incidence of

ventricular rupture. Although this is most probably not attributable to the procedure itself and this has not been observed in our own experiments or in those reported by others, most reports of ventricular rupture as well as our own recently analyzed experience indicate that ventricular rupture through the infarct is an unusual complication of acute myocardial infarction with shock. By far the great majority of ruptures have occurred as sudden events in patients with acute myocardial infarction who were not in shock and who showed hemodynamic stability just prior to the rupture. Interpretation of the ultimate clinical benefits of the procedure is also made difficult by the fact that patients who received circulatory assistance also received large quantities of intravenous fluids, which can favorably affect the arterial pressure. While analysis of the results by separation of the previously mentioned clinical groupings of shock patients may be somewhat arbitrary and the majority of patients with cardiogenic shock studied to date have not had ultimate reversal of their fatal clinical course some patients with advanced apparently refractory shock have benefited from the procedure.

More pessimistic conclusions may be drawn from the recently reported results of Summers and associates concerning intraaortic balloon pumping in patients with cardiogenic shock. In their 5 carefully studied patients refractory to conventional medical management, hemodynamic improvement was obtained by balloon pumping in all. However no patient survived and each had severe triple vessel coronary artery disease and poor collateral circulation as determined by coronary arteriography. There was a large, poorly contracting left ventricle in each instance. These findings suggest that even more radical therapy such as infarctectomy might have to be considered in the future management of these patients.

Future trends

From this brief review of the current status of circulatory support with diastolic augmentation it is obvious that our present knowledge concerning the ultimate benefits of these devices is scanty. What is required is careful hemodynamic evaluation of patients with shock following acute myocardial infarction and if possible the early separation of these patients into prognostic categories so that circulatory support, if it is to be used may be employed before irreversible circulatory deterioration has occurred. It is of key importance to realize that patients with the shock syndrome may present different hemodynamic disturbances even though they may have many common clinical features. Therefore, instead of advocating the broad use of a specific circulatory support device for all patients with cardiogenic shock refractory to medical management, it would be well to focus on the principal hemodynamic abnormalities observed. Patients with shock with significant volume overloading of the left ventricle whose principal manifestation is congestive heart failure may be expected to benefit more from techniques of left ventricular bypass or direct left ventricular drainage than from aortic balloon diastolic augmentation. Those with progressive, severe hypotension as the major presenting syndrome will probably derive more benefit from techniques to raise the aortic pressure, such as aortic balloon diastolic augmentation. Combinations of these techniques would appear to be rational when combined hemodynamic abnormalities are present. The adjunctive use of hyperbaric oxygenation to provide more myocardial oxygen and possibly hypothermia, to diminish myocardial oxygen requirement may also be helpful but critical clinical data to establish this are not available at this time.

Finally it appears that in view of the continuing high mortality in this syndrome it is appropriate to consider the feasibility of a carefully studied series of patients with unresponsive cardiogenic shock who are maintained temporarily with circulatory support, while coronary arteriography and left ventriculography are performed with a view toward therapeutic infarctectomy (or aneurysmectomy) and/or coronary arterial bypass or myocardial revascularization procedures. This is the time for increasingly close cooperation among the disciplines of

cardiology cardiovascular surgery and engineering

Summary

The hemodynamic effects of alteration of the aortic pressure pulse by diastolic augmentation in experimental acute myocardial infarction and clinical experience with these techniques are described

Both counterpulsation of blood in the aorta or femoral arteries and phased inflation of a thoracic aortic balloon achieve with reasonable predictability the physical aims of the procedure i e diminution of the aortic systolic pressure and increment of the aortic diastolic pressure However varying hemodynamic consequences of these effects have been reported in experimental acute myocardial infarction with shock Despite theoretical considerations significant increase of the diminished coronary flow has not been found uniformly particularly when the initial aortic pressure is quite low Oxygen consumption of the myocardium usually but not invariably has been lowered by this technique and variable effects have been reported in reversing the anaerobic myocardial metabolic alterations of acute myocardial infarction Analysis of the results indicates that the technique achieves optimal physiologic efficacy when it operates with a substrate of adequate central aortic pressure This is accomplished more readily with balloon pumping than with central aortic counterpulsation of blood alone probably because of some circulatory compartmentalization produced by the balloon as well as by its central aortic pumping effects In addition balloon pumping as compared to counterpulsation of blood affords the advantage of easier peripheral arterial cannulation and less destruction of the formed elements of the blood thus allowing it to be used for longer periods When the arterial pressure is quite low additional efficacy can be obtained by utilizing the technique with a method to raise central aortic pressure by means of circulatory compartmentalization with a distal aortic balloon

The clinical results have been too sparse to form valid conclusions concerning the indications for and the ultimate hazards and benefits of the techniques in acute myocardial infarction with shock. Most of the available experience has been with phase inflation and deflation of a helium-filled thoracic aortic balloon This has indicated a variable survival rate (about 30 per cent in the largest series) in patients refractory to conventional medical management. It is stressed that it is necessary to obtain more precise prognostic indications in acute myocardial infarction in the future so that optimum and reasonably early selection of patients who will not respond to other forms of therapy may be accomplished. This may permit initiation of circulatory support before irreversible cardiovascular deterioration has occurred

REFERENCES

1 Hahnloser P B Gallo, E. and Schenk, W G. Jr The hemodynamics of counterpulsation J Thorac. Cardiovasc. Surg. 51:366, 1966.
2 Hirsch L. J Lluch A., and Katz, L. N Counterpulsation effects on coronary blood flow and cardiac oxygen utilization, Circ. Res. 19:1031 1966.
3 Jacobey J A. Craddock, L. D Wolf P S and Beckwitt, H J Clinical experience with counterpulsation in coronary artery disease J Thorac. Cardiovasc. Surg 56:346, 1968.
4 Kantrowitz A., Krakauer J S Butner A. N Freed P S Jaron, D Rosenbaum, A., and Goodman, P M Phase-shift balloon pumping in cardiogenic shock, Progr Cardiovasc. Dis. 12:293 1969
5. Kuhn L. A. Kline H J Marano, A. J Cohn, L. J Weinrauch, H and Berger M Hemodynamic and cardiac metabolic effects of mechanical increase of vascular resistance in experimental myocardial infarction with shock, Circ. Res. 19:1056 1966.
6. Kuhn, L. A. Unger A. Novick, S. Steinhouse, K. Marano, A. and Abrams, A. Effects of combined central aortic counterpulsation and balloon aortic obstruction in myocardial infarction with shock Circulation 38 VI 120, 1968.
7 Kuhn, L. A. Unger A. E., Novick, S A., Marano, A. J and Rosenberg A. Hemodynamic and cardiac metabolic effects of diastolic intra-aortic balloon obstruction combined with distal aortic "booster" occlusion in experimental acute myocardial infarction with shock, Amer J Cardiol. 25:111 1970. (Abst.)
8. Moulopoulos, S. D Topaz, S. and Kolff W J: Diastolic balloon pumping (with carbon dioxide) in the aorta—a mechanical assistance to the failing circulation, Amer. Heart J 63:669 1962.
9 Powell W J Jr Daggett, W M Magro, A. E., Bianco, J A. Buckley M J Sanders, C. A., Kantrowitz, A. R., and Austen, W G.

Effects of intra-aortic balloon counterpulsation on cardiac performance, oxygen consumption, and coronary blood flow in dogs, Circ. Res. 26 753 1970

10. Rosensweig, J and Chatterjee, S.: Treatment of acute myocardial infarction by counterpulsation. Experimental rationale and clinical experience, J Thorac. Cardiovasc. Surg. 59:243 1970.

11. Summers, D N Kaplitt, M Norris, J Rubin, R., Nacht, R., Arieff A., Lee, M Wechsler B and Sawyer P N Intra-aortic balloon pumping Hemodynamic and metabolic effects during cardiogenic shock in patients with triple coronary artery obstructive disease, A.M.A. Arch. Surg. 99 733, 1969

12. Talpins, N L., Kripke, D. C., and Goetz, R. H.: Counterpulsation and intraaortic balloon pumping in cardiogenic shock, circulatory dynamics, A.M.A. Arch. Surg. 97:991 1968.

13. Tanaka, S., Rossman, W., Lande, A., Kaster R., and Lillehei, C. W Cardiovascular responses of the failing dog heart to counterpulsation, J Thorac. Cardiovasc. Surg. 58 112, 1969

14. Tyberg, J V Keon, W J Sonnenblick, E. H., and Urschel, C. W Effectiveness of intra-aortic balloon counterpulsation in the experimental low output state, Amer Heart J 80:89 1970.

Annotations

Treatment of ventricular arrhythmias with bretylium tosylate*

The purpose of this communication is to reinforce the clinical usefulness of bretylium tosylate in the management of ventricular arrhythmias.

Bretylium received clinical trial in the late 1950's as an antihypertensive agent. Tolerance develops quite rapidly to the hypotensive action of bretylium.[1] Its major side effect is postural hypotension in man which is presumably due to the sympathetic blockade which mediates the venoconstrictor response that supports venous return when the upright position is taken.

The pharmacology and clinical application of the drug related to the treatment of ventricular arrhythmias has been described by Bacaner.[2,3] Bretylium will elevate threefold the threshold required to electrically induce ventricular fibrillation in the dog. In contrast to the other antiarrhythmic drugs, bretylium has a positive inotropic effect and sensitizes the myocardium to endogenous catecholamines. In a clinical study of 30 consecutive patients, bretylium appeared to be effective in terminating ventricular arrhythmias usually within 5 minutes to several hours; the antiarrhythmic effect was relatively long lasting from 10 to 20 hours after a single dose.

Our initial experiences with this drug have been favorable. The first patient, a 62-year-old man, was admitted for treatment of atrial fibrillation and paroxysmal ventricular tachycardia. No myocardial infarction was documented. Treatment of his heart failure with conventional therapy failed to terminate the arrhythmia despite lidocaine, pronestyl, glucagon, and propanolol therapy. Transvenous right ventricular pacing was only temporarily effective. On the ninth day, he was started on intravenous bretylium. He received 1,200 mg. over 31 hours. Four months later the patient still had no recurrences of ventricular tachycardia. The atrial fibrillation was unaffected.

The second patient, a 63-year-old man with one previous myocardial infarction, was admitted with an acute inferior wall myocardial infarction complicated by moderate congestive heart failure, first degree A-V block, and infrequent premature ventricular contractions. On the fifth day, he developed ventricular fibrillation. Direct current shock was applied 5 times with concomitant bicarbonate therapy, external cardiac massage, tracheal intubation, and lidocaine therapy. He could not be defibrillated until 300 mg. of bretylium tosylate were given intravenously, after which a stable normal sinus rhythm was maintained for the next 5 days. His blood pressure, which was unobtainable with his ventricular fibrillation, remained low after defibrillation. On the sixth day, he became normotensive, but on the eighth day, he again became hypotensive with severe congestive heart failure. He was unresponsive to standard medical therapy and died. Postmortem examination showed a recent inferoposterior wall myocardial infarction, an old extensive anteroseptal and lateral wall myocardial infarction, total occlusion of the distal right coronary artery, and partial occlusion of the anterior descending and circumflex arteries.

Bretylium tosylate was apparently effective in the treatment of ventricular tachycardia and fibrillation in both of these cases. Although the exact mechanism of action is unknown, its advantage over other antiarrhythmic drugs would be its positive inotropic effect coupled to its antiarrhythmic action.

No significant complications were obvious although in the second case, the initial hypotension may have been due to bretylium.

Since the time of this writing, several other patients have received bretylium tosylate with favorable results. We hope to report in detail the results in the near future.

Joseph I. Krell, M.D.
Louis Rakita, M.D.
Faculty of Medicine,
Case-Western Reserve University
at Cleveland Metropolitan General Hospital
Cleveland, Ohio

*Present address: Mt. Sinai Hospital of Cleveland, Cleveland, Ohio 44106.

REFERENCES

1. Collery, C. T., et al.: Lancet 2:261, 1969.
2. Bacaner, M. B.: Treatment of ventricular fibrillation and other acute arrhythmias with bretylium tosylate, Amer. J. Cardiol. 21:530, 1968.
3. Bacaner, M. B.: Quantitative comparison of bretylium tosylate with other antifibrillatory drugs, Amer. J. Cardiol. 21:504, 1968.

*Kindly supplied by Burroughs, Wellcome and Company.

Milk protein and other food antigens in atheroma and coronary heart disease

Cow milk protein is now implicated in the causation of coronary heart disease. This is the result of chain of investigations and deductions culminating in the observation that the serum level of antibodies to reconstituted heat-dried cow's milk is significantly increased in this disease (Davies and associates[1]). It is now possible t combine the thrombogenic and filtration concepts into one immunological hypothesis. Many facts about atheromatous occlusive vascular disease previously appearing unrelated can now be integrated and explained and there are fundamental prophylactic and therapeutic implications.

The work originated from observing that the negative electric charge on circulating erythrocytes, in coronary heart disease, is reduced and that this is due to an abnormality of the plasma. This observation led to series of experiments[2-4] which indicated that ll circulating particles are similarly affected causing them to be abnormally adhesiv. Increased platelet adhesiveness in coronary heart disease is the result of this abnormality of plasma surface activity reducing the size of the normal negative electric charge upon the surface of the platelet.

Finding an increase in an immunoglobulin (IgG) in coronary heart disease[5] led to realization that this pathological adhesiveness could be an example of immunoadherence[6] this then initiated a search for possible causative antigens. The first clinical evidence of this disease is frequently in previously healthy person. This suggested that the antigenic stimulus is not endogenous, which ould be expected to cause symptoms, and possible exogenous antigens ere therefore considered. Dietary proteins can be antigenic, enough whole protein being absorbed from the gastrointestinal tract to actuate immunological mechanisms. It is hy considerable proportion of the apparently normal healthy population have serum antibodies t cow milk protein. This ppears to be lifelong happening[10,11] and t is to be expected that such individuals ill from time to time produce circulating antigen-antibody immune complexes following ingestion of milk, the probability of this occurring being greater in individuals with higher titer. Immune complexes are known to activate vascular endothelium[12] and promote deposition of platelets and fibrin. They can be taken p by platelets causing them t aggregate[13] and form thrombus. It follows that the increase in serum milk antibodies in coronary heart disease can explain coronary thrombosis.

Considerable evidence shows that lipoproteins normally filter through the arterial all the lipid accumulation found in atheromatous lesions may be due to derangement in this process. This abnormality can be explained by the action of circulating immune complexes for they activate mast cells to release histamine and 5-hydroxytryptamine which increase vascular permeability.

I addition to these tw fundamental processes other important features of therogenesis explainable upon an immunological basis[4] are the role of smooth muscle in the arterial wall,[14] the relationship of mast cells to coronary heart disease,[15-17] the variable susceptibility of arterial tissue to atheroma,[18] and the occurrence of phasic activity

The mortality rate for arteriosclerotic heart disease in England and Wales shows seasonal pattern. The winter excess of deaths in any particular year is very highly correlated with coldness.[19] An association has been demonstrated within the United States between coronary mortality rates and the mean temperature of the locality.[20] The levels of serum milk antibody found when samples of patients are tested appear to bear relationship to this phenomenon. For it has been found (unpublished data for Southwest Wales) that much higher percentage of sample of patients developing myocardial infarction during the summer months has b- normally high milk antibody level tha does sample of similar patients taken ill during the winter months. It would appear that the cold of winter provides some further independent causative factor.[20]

Atheroma is found in all and is due t progressive process which is lifelong but variable in rapidity of development. It is t be expected that the causative process is more activ when an occlusive manifestation occurs in the young than it is in patients developing occlusion only in the later years of life. It follow that the investigation of coronary heart disease may be more rewarding when made of younger patients. This ppears to be true for serum milk antibody levels, for when male patients under 60 years of age who develop infarction during the summer months are investigated, a highly significant increase in antibody titer is found. But from the data as yet vailable, there appears to be little if any difference between patients and matched controls over this age. It may be that the higher the antibody level, then the earlier does death occur from atheromatous disease the data are consistent ith this concept. The abnormality may well be due to an inherited metabolic disorder and it is noteorthy that in family having very high incidence of coronary heart disease all six members so far examined have milk antibody level of the order of times eight that level which can now be considered as normal (npublished data).

The increase in serum milk antibody level in coronary heart disease may also be related to artificial infant feeding with cow milk. Nearly all infants fed in this ay receive an antigenic stimulation by its proteins and become sensitized to varying degrees.[21] Breast milk does not ppear to have any such comparable effect. The age t which exposure to the antigenic influence of cow milk protein first occurs influences the immunological response.

For there is evidence that breast feeding results in a lower serum antibody level to cow's milk protein when this is ingested later in life, than does artificial feeding with cow's milk products.[22,23] It is likely that these findings are related to those of Osborn.[19] The mothers of 109 young individuals whose coronary arteries had been studied were questioned about postnatal feeding. Where there had been no breast feeding he found that the coronary arteries were mainly abnormal. Those with at least two months breast feeding mostly had normal coronary arteries. Thought must now be given to the possibility that artificial feeding with heat-dried cow's milk preparations is creating an immunological basis for atherosclerotic disease.

The data suggest that the abnormal increase in serum level of antibodies in coronary heart disease is maximal to heat-dried cow's milk and minimal to unheated cow's milk. It is possible heat treatment renders cow's milk protein less acceptable immunologically. There is some support for this from world surveys of the distribution of atherosclerotic disease and the type of diet consumed.[25] It is also noteworthy that myocardial infarction has been found to be twice as common in peptic ulcer patients on a milk diet than in either those not treated with milk or in control patients.[26]

At present milk protein is the only antigen found to be involved but there may well be others. Circulating antibodies to dietary antigens such as gluten and egg albumin can be demonstrated in a considerable proportion of normal subjects. Now raised by this series of observations [illegible] the new concept that lifelong absorption of any food antigen in susceptible individuals may lead to atheromatous disease. It may well be that the responsible antigens vary among individuals, races, and species.

The immunological hypothesis does not conflict in any way with that implicating abnormal serum levels of cholesterol and other lipids nor does it conflict with therapeutic attempts to correct them. It embraces the filtration and thrombogenic theories into one concept. For the first time in this disease there is a possibility of logical preventative and therapeutic measures based upon an understanding of the underlying pathological processes. The seriousness of this disease in our societies warrants urgent attention to the hypothesis and further experimental work to substantiate it. But also consideration should be given to initiating now the determination of serum milk antibody levels both as a screening procedure in healthy individuals and as a parameter in atherosclerotic occlusive vascular disease. Abnormal sensitivity found in this way would indicate the necessity of reduced intake or abstention from cow's milk protein both in milk and in its many and varied preparations.

D. F. Davies M.D., M.R.C.P. (Lond.) M.C.Path.
Department of Pathology
West Wales Hospital
Carmarthen, Wales

REFERENCES

1. Davies, D. F.: The electrophoretic mobility of erythrocytes as a measure of the surface activity of plasma from patients with and without evidence of atheroma, Clin. Sci. 17:563, 1958.
2. Davies, D. F.: A comparison of erythrocyte and chylomicron electrophoretic migration times and serum cholesterol levels in atheroma, Clin. Sci. 18:263, 1959.
3. Davies, D. F., and Clark, A.: An assessment of erythrocyte migration times and serum cholesterol levels as indices in myocardial infarction, Clin. Sci. 20:279, 1961.
4. Davies, D. F.: A new theory relating atherogenesis and coronary heart disease to impairment of plasma surface activity, Amer. Heart J. 70:720, 1965.
5. Davies, D. F., and Lloyd, V.: Relationship between platelet adhesiveness and plasma surface activity in coronary heart disease, Cardiovasc. Res. 1:108, 1967.
6. Davies, D. F., and Clark, A.: Increase of γG-globulin in coronary heart disease, J. Atheroscler. Res. 8:724, 1968.
7. Davies, D. F., Davies, J. R., and Richards, M. A.: Antibodies to reconstituted dried cow milk protein in coronary heart disease, J. Atheroscler. Res. 9:103, 1969.
8. Davies, D. F.: An immunological view of atherogenesis, J. Atheroscler. Res. 10:253, 1969.
9. Nelson, D. S., *in* Dixon, F. J., and Humphrey, J. H., editors: Advances in immunology, vol. 3, New York and London, 1963, Academic Press, p. 131.
10. Schloss, O. M.: The intestinal absorption of antigenic protein, Harvey Lecture Series 20:156, 1924-1925.
11. Gell, P. G. H., and Coombs, R. R. A.: Clinical aspects of immunology, Oxford and Edinburgh, 1968, Blackwell Scientific Publications, p. 1036.
12. Biozzi, G., Mene, G., and Ovary, Z.: Rev. Immunol. (Paris) 1:320, 1948.
13. Gell, P. G. H., and Coombs, R. R. A.: Clinical aspects of immunology, Oxford and Edinburgh, 1968, Blackwell Scientific Publications, p. 725.
14. Scott, R. F., Daoud, A. S., Wortman, B., Morrison, E. S., and Jarmolych, J.: Proliferation and necrosis in coronary and cerebral arteries, J. Atheroscler. Res. 6:499, 1966.
15. Paterson, J. C., and Mills, J.: Myocardial mast cell counts in coronary sclerosis, Arch. Path. 66:335, 1959.
16. Pomerance, A.: Peri-arterial mast cells in coronary atheroma and thrombosis, J. Path. Bact. 76:55, 1958.
17. Pepler, W. J., and Meyer, B. J.: Mast cells in the coronary arteries, Arch. Path. 71:209, 1961.
18. Haimovici, H., and Maier, N.: Role of arterial tissue susceptibility in experimental canine atherosclerosis, J. Atheroscler. Res. 6:62, 1966.
19. Osborn, G. R.: The incubation period of coronary thrombosis, London, 1963, Butterworth & Co. Ltd.
20. Rose, G.: Cold weather and ischaemic heart disease, Brit. J. Prev. Soc. Med. 20:97, 1966.
21. Moriyama, I. M., and Herrington, L. P.: Amer. J. Hyg. 28:423, 1938.
22. Gunther, M., Aschaffenburg, R., Mathews, R. H., Parish, W. E., and Coombs, R. R. A.:

The level of antibodies to the proteins of cow' milk in the serum of normal human infants, Immunology 3:296, 1960.
23. Gunther M Cheek, R., Mathews, R. H., and Coombs, R. R. A. Immune responses in infants to cow milk protein taken by mouth, Int. Arch. Allergy 21:257 1962.
24. Osborn, G. R. Stages in development of coronary disease observed from 1,500 young subjects, in Le rôle de la paroi artérielle dans l' athérogénèse, Colloques I ternationaux du Centre National de la Recherche Scientifique, Paris, 1968, Éditions d Centre National de la Recherche Scientifique.
25. Annand, J C. Hypothesis: Heated milk protein and thrombosis, J Atheroscler Res. 7 797 1967
26. Briggs, R. D : Myocardial infarction in patients treated with Sippy and other high milk diets. Circulation 21:538, 1960.

Right bundle branch block and right axis deviation in patients with coronary artery disease

Within recent years, the etiological basis and significance of various intraventricular conduction disorders have been more precisely defined as a result of careful pathologic, clinical, and electrocardiographic correlative studies[1-4] The relationship of right bundle branch block (RBBB) and marked left axis deviation (LAD) to complete heart block and syncope, for example has been well demonstrated particularly in older patients with coronary artery disease. This conduction defect has been ascribed to pathologic block below the bundle of His involving the main right bundle and the superior or anterior division of the main left bundle subsequent to diffuse fibrosis, necrosis, or infarction[1,3,5-9] It represents, in essence, an incomplete bilateral bundle branch block since the inferior division of the left bundle remains the only portion of the specialized conduction system physiologically intact for the transmission of supraventricular impulses to the ventricles. This may (very) well explain its tendency to progress to complete bilateral bundle branch block with its serious clinical implications and sequelae. Indeed, recent study has shown that the risk of developing complete heart block in an unselected series of patients with RBBB and LAD to be about 10 per cent. Moreover 60 per cent of such patients showed this pattern either before the development of chronic complete heart block or following recovery from transient block.

On the other hand, little has been written about the genesis and prognostic significance of acquired RBBB and right axis deviation (RAD) in patients with latent or overt coronary artery disease. This combination of conduction defects also represents, as does RBBB and LAD an incomplete bilateral bundle branch block due to block of the main right bundle and the posterior or inferior division of the left bundle Its clinical implications, namely the high risk of developing bilateral bundle branch block, would therefore be the same as that of RBBB and *LAD* since only one fascicle of the left bundle remains intact.

I order to consider the significance of acquired RBBB and RAD in the setting of coronary artery disease, tx other causes of this conduction defect must be excluded. It may be found not infrequently for example, in patients with right entricular hypertrophy secondary to variety of congenital and acquired cardiovascular disorders in which either a significant elevation of the pulmonary artery pressure or obstruction of the outflow tract of the right ventricle is present. This also includes its sudden appearance in cases of acute pulmonary embolism and high altitude pulmonary edema with reversibility after return of normal pulmonary vascular hemodynamics. In this context, the electrocardiographic features of RBBB and RAD are compatible with the diagnosis of RVH and merely denotes a unifascicular block that is of the right bundle alone, since the RAD is the consequence of right ventricular hypertrophy and not of block of the inferior division of the left bundle

Patients with advanced pulmonary disease, whether of the restrictive or obstructive type, may also demonstrat RBBB and RAD I these cases the combined conduction defect also represents unilateral block of the right bundle since the RAD is the result of "verticalization of the QRS forces due to diminished conductance of the lungs and the effect of lowered diaphragm with or without coexistent cor pulmonale.

I patients with coronary artery disease, on the other hand, the pathogenesis and significance are quite different. Here it is related to a pathologic lesion of the right bundle and inferior division of the left bundle, due to significant ischemia produced by an impaired coronary vascular supply

The more frequent occurrence of RBBB and LAD than RBBB and RAD in coronary artery disease may be explained by the anatomy of the specialized conduction system of the myocardium and its blood supply Anterior wall infarction, particularly anteroseptal infarction, would more readily produce complete RBBB, since the middle third of the right bundle is nourished almost exclusively from the anterior perforating branches of the left anterior descending artery. Left axis deviation may also develop simultaneously since

For there is evidence that breast feeding results in a lower serum antibody level to cow's milk protein, when this is ingested later in life, than does artificial feeding with cow's milk products.[22,23] It is likely that these findings are related to those of Osborn.[19] The mothers of 109 young individuals whose coronary arteries had been studied were questioned about postnatal feeding. Where there had been no breast feeding he found that the coronary arteries were mainly abnormal. Those with at least two months breast feeding mostly had normal coronary arteries. Thought must now be given to the possibility that artificial feeding with heat-dried cow's milk preparations is creating an immunological ba i for atherosclerotic disease.

The data suggest that the abnormal increase in serum level of antibodies in coronary heart disease is maximal to heat-dried cow's milk and minimal to unheated cow's milk. It is possible heat treatment renders cow's milk protein less acceptable im munologically There is some support for this from world survey of the distribution of athero-sclerotic disease and the type of diet consumed.[25] It is also noteworthy that myocardial inf rction has been found to be twice as common in peptic ulcer patients on a milk diet than in either those not treated with milk or n control patients.[26]

At present milk protein is the only a tigen found to be involved but there may well be others. Circu lating antibodies to dietary ant gen such a gluten and egg albumi can be demonstrated i a consider able proportion of normal subjects. Now r sed by this series of observations [1-8] is the new concept that lifelong absorption of any food ant gen in susceptible ind viduals may lead to atheromatous disease. It may well be that the responsibl ntigens vary among ind viduals races, a l pecies.

The mmunological hypothes does not conflict in any w y with that implicating abnormal serum levels of cholesterol and other l pid nor does it conflict with therapeutic attempts to correct them It embraces the filtration and thrombogenic theories into one concept. For the fir t time n this disease there is a possibility of logical preventative and therapeutic measures based upon an underst nding of the underlying pathological processes. The seriousness of this disease in our societies, warrants urgent attention to the hypothesis and further experimental work to substantiate t. But also consideration should be given to initiating now the determination of serum milk antibody levels both as a screening procedure in healthy individuals and as a parameter in atherosclerotic occlusive vascular disease. Abnormal sensitivity found in this way would indicate the necessity of reduced intake or abstention from cow's milk protein both in milk and in its many and varied preparations.

D F Davies, M.D., M.R.C.P (Lond) M C.Path.
Department of Pathology
West Wales Hospital
Carmarthen, Wales

REFERENCES

1. Davies, D F The electrophoretic mobility of erythrocytes as a measure of the surface activity of plasma from patients with and without evidence of atheroma, Clin. Sci. 17:563, 1958.
2. Davies, D F: A comparison of erythrocyte and chylomicron electrophoretic migration times and serum cholesterol levels in atheroma, Clin. Sci. 18:263 1959
3. Davies, D F., and Clark, A. An assessment of erythrocyte migration times and serum cholesterol levels as indices in myocardial infarction, Clin. Sci. 20:279 1961
4. Davies, D F A new theory relating atherogenesis and coronary heart disease to impairment of plasma surface activity Amer. Heart J 70:720, 1965
5. Davies, D F and Lloyd V Relationship between platelet adhesiveness and plasma surface activity in coronary heart disease Cardiovasc. Res. 1:108, 1967
6. Davies, D F., and Clark, A. Increase of γG-globulin in coronary heart disease, J Atheroscler Res. 8:724 1968.
7. Davies, D F Davies, J R. and Richards, M A. Antibodies to reconstituted dried cow's milk protein in coronary heart disease, J Atheroscler Res. 9 103, 1969
8. Davies, D F An immunological view of atherogenesis, J Atheroscler Res. 10:253 1969
9. Nelson, D S. in Dixon F J and Humphrey J H editors Advances in immunology vol. 3, New York and London, 1963 Academic Press, p. 131
10. Schloss, O M The intestinal absorption of antigenic protein, Harvey Lecture Series 20:156 1924-1925
11. Gell P G H and Coombs, R R. A. Clinical aspect of immunology Oxford and Edinburgh, 1968 Blackwell Scientific Publications, p. 1036.
12. Biozzi, G Mene G and Ovary Z: Rev Immunol (Paris) 12:320 1918.
13. Gell P G H and Coombs, R. R. A. Clinical aspects of immunology Oxford and Edinburgh 1968, Blackwell Scientific Publications, p. 725.
14. Scott, R. F Daoud A. S. Wortman, B., Morrison E. S. and Jarmolych, J: Proliferation and necrosis in coronary and cerebral arteries, J Atheroscler Res. 6:499 1966.
15. Paterson, J C. and Mills, J: Myocardial mast cell counts in coronary sclerosis, Arch. Path. 66:335 1959
16. Pomerance, A.: Peri-arterial mast cells in coronary atheroma and thrombosis, J Path. Bact. 76 55 1958.
17. Pepler W J and Meyer B J: Mast cells in the coronary arteries, Arch. Path 71:209 1961
18. Haimovici H. and Maier N Role of arterial tissue susceptibility in experimental canine atherosclerosis, J Atheroscler Res. 6:62 1966.
19. Osborn, G. R.: The incubation period of coronary thrombosis, London, 1963 Butterworth & Co., Ltd.
20. Rose, G. Cold weather and ischaemic heart disease, Brit. J Prev Soc. Med. 20:97 1966.
21. Moriyama, I M., nd Herrington, L. P: Amer J Hyg 28:423 1938.
22. Gunther M Aschaffenburg, R., Matthews, R. H., Parish W E., and Coombs, R. R. A.:

occasion This great problem was ultimately overcome by the introduction of the Quinton-Scribner Teflon-Silastic exteriorized arteriovenous shunt, which enables the patient to be repeatedly connected to the extracorporeal circuit without the need for repeated surgical exposure of his vessels. This external shunt has proved of value additionally in patients requiring repeated blood transfusion, as may occur in plastic anemia, when the veins have become increasingly difficult to cannulate

Unfortunately along with their great benefits, such shunts have produced their own problems such as infection, extrusion, hemorrhage, obstruction, and thrombosis Infection frequently causes loss of a valuable shunt site. It may also give rise to septicemia and septic embolism. Extrusion of the shunt may be abrupt or gradual, resulting in the need for reinsertion, often at fresh site Catastrophic hemorrhage may be accidental or deliberately produced by disconnecting the limbs of the shunt. But by far the most troublesome problem is obstruction accompanied by thrombosis.

This may result from extrinsic pressure due to dressings or to inappropriate position of the limb during sleep or travel. Intrinsic factors include intimal thickening near the cannula tip, malalignment of the cannula, and most important of all, infection, especially when due to coagulase-positive staphylococci which will produce recurrent or intractable clotting till the infection is eradicated. Other less serious causes include cold transient hypotension, and rebound hypercoagulability following heparinization.[10] Local production of thromboplastin t the site of shunt insertion, and further tissue trauma during premature hemodialyses play part in early clotting of newly inserted shunts

Obviously great pains should be taken over precautions to prevent clotting Long-term anticoagulation with warfarin sodium has been shown to be of value but care over the choice of shunt site to avoid excessive movement during activity and to minimize exposure to trauma, a delay of 10 to 14 days between insertion and hemodialysis, and early radical treatment of suspected infection are all more important. Nevertheless, despite all precautions, clotting occurs all too frequently and requires immediate attention

The techniques of declotting fall broadly into two categories, mechanical and biological. Mechanical methods consist basically of aspiration of clot by means of catheter and syringe. Much material may frequently be removed by this means despite the acuteness of the bends of the subcutaneous portion of tubing. The arterial limb can often be cleared completely by combination of this technique and simple suction by syringe directly attached to the tubing. The venous limb less frequently yields completely to aspiration, and it is often necessary to flush residual clot out the circulation by means of arm heparinized saline. Despite the apparently undesirable nature of this procedure and the obvious occurrence of pulmonary embolism, septic or sterile, there are no recorded instances of unfortunate sequelae of this exercise. In contrast, positive-pressure flushing of the arterial line in the forearm has been reported on several occasions to be followed by varying degrees of cerebral arterial insufficiency with results varying from death to transient minor functional impairment. This outcome has been attributed variously to vasospastic reactions to injection of cold fluid and t vertebral artery embolism.[11-14] Whatever the mechanism, flushing of the arterial limb of the shunt must not be undertaken without adequate precautions. We would suggest that positive pressure flushing should be undertaken only (1) after the maximum amount of clot has been extracted physically from the shunt (2) with fluid which is isotonic and warmed to 37° C. (3) with a maximum volume of fluid not exceeding 5 ml. in any single injection and (4) where high pressure has to be used, with tourniquet around the upper arm, inflated temporarily to above systolic blood pressure.

One further technique[16] is appropriate to the straight shunt[17] which can be cleared by passing up flexible spiral wire to trap the thrombus which can then be withdrawn.

The biological approach consists of the use of fibrinolytic enzymes to liquify thrombus which can then be readily cleared by flushing. Such enzymes are of three kinds. Streptokinase[17,18] has been shown to be effective when infused into the shunt. A solution of 250 000 units in 250 ml. over a period of six hours is frequently useful. However being product of bacterial origin, it carries significant risk of anaphylactic reactions as well as occasionally producing hemorrhagic manifestations. Some workers always pretreat with steroids before giving streptokinase.

Protease I[19,20] is a proteolytic enzyme derived from *Aspergillus oryzae* and can produce severe pain and necrosis if allowed to leak into the perivascular tissues.

Urokinase is a fibrinolytic agent derived from human urine, and so is poorly antigenic. It has the disadvantage of being expensive, which makes it suitable mainly for topical or closed-space application in low dosage but fairly high concentration. We[21] have used dose of 5,000 Ploug (7 000 Committee on Thrombolytic Agents) units dissolved in about 5 ml. of warm saline and instilled into the occluded shunt limb which is then clamped and left undisturbed for up to one hour. When possible a shunt angiogram has first been obtained and based on the angiographic appearances, the volume of solution used has been adjusted. Where significantly more than 5 ml. seems indicated, 10,000 units of enzyme may be used. The results from limited series of patients are shown in Table I

Of the seven patients receiving urokinase, five had prolongation of shunt life by periods ranging from 17 to 88 days, using urokinase on more than one occasion. The two most lasting successes occurred where staphylococcal infection yielded to cloxacillin. A third patient had similar infection which failed to respond to antibiotics and the shunt was lost at 17 days, while mechanical factors in the other two caused them to fail also on the seventeenth day

It is clear that fibrinolytic therapy has most to offer where infection can be readily controlled, or where transient factors such as cold, trauma, pressure, tissue thromboplastin, or heparin rebound

the anterior fascicle of the left bundle is also supplied by the same main vessel (the anterior descending coronary artery).[1-8]

Similarly ischemic necrosis of the inferior posterior division of the left bundle may develop when an occlusive lesion involves the right coronary artery and its posterior perforating branches. On the other hand RBBB would not readily develop in right coronary artery disease so long as its main source of nourishment—the left anterior descending artery—remains intact. Its occurrence in the setting of posterior and/or inferior wall infarction, although less frequent may be explained as follows (1) a widespread infarction with extension well into the interventricular septum toward the more anterior location of the right bundle (2) simultaneous occlusion of the anterior perforating branches of the left coronary artery or (3) presence of RBBB prior to the occurrence of acute infarction.

Thus the significance of RBBB and RAD in patients with coronary artery disease can be properly appreciated if other causes of this pattern, such as RVH and pulmonary disease have been excluded. First, it should be recognized as an incomplete bilateral bundle branch block (RBBB and left posterior hemiblock) and, second the presence of significant coronary artery disease with variable degree of infarction in the posterior and/or inferior wall should be strongly implied as the underlying cause of this conduction defect.

Indeed our preliminary vectorcardiographic study of patients with RBBB and RAD and evidence of coronary artery disease on the basis of history and clinical findings has shown a significant anterior displacement of the entire or the preponderant portion of the QRS loop in both the horizontal and sagittal planes. This represents in our opinion the reflection of direct posterior wall infarction with involvement of the posterior inferior division of the left bundle producing significant right axis deviation of the QRS forces in the frontal plane.

We believe that the potential hazard to patients with arteriosclerotic heart disease with RBBB and RAD toward the development of complete bilateral bundle branch block and its serious sequelae to be just as great as in those patients with RBBB and LAD. In both instances the only portion of the specialized conduction system that remains viable for the transmission of a supraventricular impulse for ventricular depolarization is only one fasciculus of the left bundle. It would seem logical that the potential for a lesion to develop in either the remaining superior or inferior division of the left bundle to be equal. Follow-up clinical studies will be necessary however to confirm this impression.

We therefore strongly advise close and repeated follow up of all patients with arteriosclerotic heart disease who demonstrate RBBB and RAD for the detection of any signs of atrioventricular block and recommend insertion of a permanent pacemaker in the event second or third degree A V block develops. If RBBB and RAD emerge as a result of an acute myocardial infarction, we recommend the placement of a temporary transvenous pacemaker of the demand type which would become operative in the event A V block develops.

Philip Varriale Lieutenant Colonel
Chief Cardiology Service
Irwin Army Hospital
Fort Riley Kan.
Richard J Kennedy M.D.
Chief of Cardiology
St Vincent's Hospital and Medical Center
New York N Y

REFERENCES

1. Lenègre J Etiology and pathology of bilateral bundle branch block in relation to complete heart block Progr Cardiovasc. Dis. 6:409 1964
2. Lepeschkin, E. Electrocardiographic diagnosis of bilateral bundle branch block in relation to heart block, Progr Cardiovasc. Dis. 6:445 1964.
3. Uhley H N and Rivkin, L. M Electrocardiographic patterns following interruption of the main and peripheral branches of the canine left bundle of His, Amer J Cardiol. 13 41 1964.
4. Grant R. P Left axis deviation. An electrocardiographic—pathologic correlation Circulation 14:233 1956.
5. Lasser R P Haft, J I and Friedberg C. K. Relationship of right bundle branch block and marked left axis deviation (with left parietal or peri-infarction block) to complete heart block and syncope Circulation 37:429 1968.
6. Lev M The normal anatomy of the conduction system in man and its pathology in atrio-ventricular block. Ann. N Y Acad. Sci. 111:817 1964
7. James, T N The coronary circulation and conduction system in acute myocardial infarction, Progr Cardiovasc. Dis. 10:410, 1968.
8. Lev M Unger P N Lesser M and Pick, A. Pathology of the conduction system in acquired heart disease. Complete right bundle branch block. Amer Heart J 61:593 1961
9. Sutton, R. and Davies, M.: The conduction system in acute myocardial infarction complicated by heart block, Circulation 38:987 1968.
10. Rosenbaum M B. et al.: Five cases of intermittent left anterior hemiblock, Amer J Cardiol. 24:1 1969

Declotting of Quinton-Scribner shunts

With the introduction by Kolff and Berk of the artificial kidney repeated hemodialysis as a means of [illegible] came a nephrologist' goal tantalizingly unattainable because of the limitations imposed by the need for fresh cannulation [illegible]

due to de-clotting of arteriovenous shunts, Proceedings of the IVth International Congress of Nephrology 1969 In press.
14. Gaan, D Mallick, N P Brewis, R. A. L., Seedat, Y K., and Mahoney M P Cerebral damage from de-clotting Scribner shunts, Lancet 2 77 1969
15. Shaldon, S and Baillod, R. A. Proc European Dialysis Transplant Ass., 1969 (Unpublished discussion)
16. Giovannetti, S. Cioni, L., Maggiore, Q Balestri, P L., and Biagini, M A clot-screw for the winged-in line shunt, Proc. European Dialysis Transplant Ass. 4:363 1967
17. Ramirez, O., Swartz, C., Onesti, G., Mallory, I and Brest A. H. The winged-in line shunt, Trans. Amer Soc Artif. Intern Organs 12:220, 1966.
18. Anderson, D C., Martin, A. M Clunie, G. J A Stewart, W K., and Robson, J S. Eight months experience in the use of streptokinase locally for de-clotting arteriovenous cannulae, Proc European Dialysis Transplant Ass. 4:55 196
19. Kjellstrand C. M Lindergard, B., and Boijsen, E.: Treatment of clotted Quinton-Scribner arteriovenous shunts by streptokinase, Proc. European Dialysis Transplant Ass. 4:61 1967
20. Bennhold, I Froese, P Scholz A., and Kemel M Shunt de-clotting with new locally applied thrombolytic gent, Proc. European Dialysis Transplant Ass. 5:150, 1968.
21. Bucht, H. Discussion on paper by Bennhold et al[20] Shunt de-clotting with a new locally pplied thrombolytic agent, Proc. European Dialysis Transplant Ass. 5:150, 1968.
22. Witt, D A. L., Dunn, B. P., Livingstone, W R., Macdougall, A. I Mackay R. K. S., Obineche, E. N and Rennie, J B The use of urokinase in de-clotting of arteriovenous shunts, Proc. European Dialysis Transplant Ass. 6:88, 1969
23. Dathan, J R., Thomson, J M. A., and Worthington, B S. Angiographic studies of Quinton-Scribner arteriovenous cannulae, Brit. Med. J 4:20, 1969
24. Cimino J E. Discussion on methods of access to the circulation for haemodialysis, Trans. Amer Soc. Artif I tern. Organs 12:227 1966.

Table I Urokinase results in treatment

Patients given urokinase (No)	Urokinase applications (No)	Failure (No)	Success		
			Immediate (No)	1 day (No)	7 days (No)
7	27	4	23	15	6

resl tant infection occur the benefit of uch treat ment it best w ll be temporary

Shu t thrombosis i major hazard in the life of the patient on hemodialysis. Treatment, to be effective m t be undertaken at the e rliest oppor tunity by a killed operator The p tie t must be trained to recognize the signs of clotting, and to appreciate the urgency of the situation. Venous occlusion can be treated with relative safety but declotting of the rterial cannula requires caution. Irrigation fluid must be warmed. Fibrinolytic gents have only a limited place The use of teroids in conj inction with treptokinase hould be carefully considered Urokinase is safe nd re sonably effec tive and is our opi on the fibrinolytic gent of choice Recurrent thrombos ment shunt angiog raphy[12] to identify local mech ic il f ctors caus ng obstruction whi h may permit or shunt revision before the site i irretriev ibly lost Where no uch factor ca be identified infection should be ssumed to be present and warr nt immediate a tib tic treatment imed t eradic ting co g lase producing staphylococci without wa t ng bacteriolog cal confirmation By this means, h t whose survival has been jeopardized may be saved

Neverthele by virtue of t design the Qui ton Scribner shu t will l ays tend to prod ice clotting problems, nd difficulty in declotting Where the site is suitable the R mirez str ght shunt poses fewer problem both by its lesser tendency to produce tosis and by its greater ease of declotting nd may be preferred for these re sons. Perhaps how ever the incre singly popular Cimino-Brescia subcutaneous arteriovenous fi tula,[13] in which both sepsis and thrombosis are uncommon, points the w y to future development which may eventually render obsolete all form of exteriorized communication

Douglas 1 L. Watt M R C P
Brian P Dunn M B
H R Livingstone M B
A I Macdougall M R C P E.
Stobhill General Hospital
Glasgow N 1 Scotland

REFERENCES

1. Kolff W J and Berk, H T J The artificial kidney—a dialyzer with a great area Acta Med Scand 117:121 1944
2. Quinton W E. Dillard D H and Scribner B H Cannulation of blood vessels for prolonged haemodialysis, Trans. Amer Soc. Art f Intern. Org ns 6 104 1960.
3. Quinton W E. Dillard D H Cole, J J nd Scribner B H Possible improvement in the technique of long term cannulation of blood vessels, Trans. Amer Soc. Artif Intern. Organs 760 1961
4. Williams B T., Blainey J D Dawson-Edwards, I Hilton, D D and Simpson, K. M Use of Quinton-Scribner arteriovenous shunt in the management of apla tic anaem a Brit. Med J 185 1967
5. Anderson D C. Emslie-Smith D MacGregor A M C. and Stewart W K. Arteriovenous shunts for transfusion, Lancet 1:509 1967
6. Curtis, J R Eastwood J R. Smith E. K. M Storey J M Verroust I J de Wardener H E. Wing A. J and Wolfson, E. M Maintenance haemodialysis, Qu rt. J Med. 38:50 1969
7. Kopp, K. F Grossman D F and Frey J The c re and ma ntenance of the Scribner Tefl n-Silastic shunt. Experience how to prevent infection, Proc. European Dialysis Transplant Ass. 1:373 1967
8. Snyder D nd Fulido, L. A method of reducing the incidence of shunt infection Abstract of the IVth International Congress of Nephrology I 194 1969
9. Papad m triou M Carrol R. N P and Kulatilake A. E. Cl tting problem with the Tefl n-Silastic arterio enou shunt in patients on regul r h emodialysis, Brit. Med. J 2 15 1969
10. Comty C M Baillod R. A and Shaldon S. 2½ years experience with a nurse-patient operated chronic dialysi unit Proc. European Dialysis T an plant A s. 4:373 1965
11. W ng A J Curtis, J R. and de Wardener H E. Reduction of clott ng in Scribner shunts by long term anticoagulation Brit. Med. J 3 143 1967
12. Hegstrom R. M Murray J S. Pendras, J I Burnell J M and Scribner B H. Haemodialysis n the treatment of chronic uraemia Tr ns. Amer Soc. Artif Intern. Organs 7:136 1961
13. Marshall V C Kincaid Smith, P and Epstein J Retrograde cerebral embolization

due to de-clotting of arteriovenous shunts, Proceedings of the IVth International Congress of Nephrology 1969 In press.

14. Gaan, D Mallick N P Brewis, R. A. L., Seedat, Y K., and Mahoney M P Cerebral damage from de-clotting Scribner sh ts, Lancet 2 77 1969

15. Sheldon, S., and Baillod, R. A.: Proc. Europea Dialysis Transplant Ass. 1969 (Unpublished discussion)

16. Giovannetti, S., Cioni, L., Maggiore, Q Balestri, P L., and Biagini, M : A clot-screw for the lnged-in line shunt, Proc. European Dialysis Transplant Ass. 4:363 1967

17. Ramirez, O Swartz, C. Onesti, G Mailloux, L., and Brest, A. H. The winged-i line shunt, Trans. Amer Soc. Artif. Intern. Organs 12:220, 1966

18. Anderson, D C., Martin, A. M Clunie, G. J A Stewart, W K., and Robson, J S. Eight months experience in the use of streptokinase locally for de-clotting arteriovenous cannulae, Proc. Europea Dialysis Transplant Ass. 4:55 1967

19. Kjellstrand, C. M Lindergard, B., and Bolj-son, E.. Treatment of clotted Quinton-Scribner arteriovenous shunts by streptokinase, Proc. European Dialysis Transplant Ass. 4:61 1967

20. Bennhold L., Froese, P Scholz, A., and Kessel M.. Shu t de-clotting with a new locally applied thrombolytic agent, Proc. European Dialysis Transplant Ass. 5:50, 1968.

21. Bucht, H. Discussion on paper by Bennhold et al.[20] Shunt de-clotting with new locally applied thrombolytic agent, Proc. European Dialysis Transplant Ass. 5:50, 1968.

22. W tt, D A. L., Dunn, B. P Livingstone, W R., Macdougall, A. I Mackay R. K. S., Oblosche, E. N and Rennie, J B. The use of urokinase in de-clotting of arteriovenous shu ts, Proc. European Dialysis Transplant Ass. 6:88, 1969

23. Dathan, J R., Thomson, J M A., and Worthington, B. S.: Angiographic studies of Quinton-Scribner arteriovenous cannulae, Brit. Med. J 4:20, 1969

24. Chalmo, J E. Discussion on methods of access to the circulation for haemodialysis, Trans. Amer Soc. Artif. Intern. Organs 12:227 1966.

Book reviews

PERIPHERAL ARTERIAL DISEASE, A Physician's Approach By Robert L. Richards, M D F R C P E D F R C P (Glasg) London, 1970 E. & S Livingstone Ltd. 126 pages Price $10 50

Richards has produced a very good and succinct discussion of peripheral arterial disease The approach is sound clinical and practical He describes the office and general hospital approach to the diagnosis and management of arterial disease of the limbs There are no frills fancy and yet unevaluated procedures of diagnosis or treatment included He clearly defines what is useful in management of these diseases and the limitations in drugs and surgery The author in this brief book displays knowledge of the subject. This reviewer warns the readers that a profound knowledge of peripheral vascular physiology and clinical medicine will be required to appreciate the full implication of the statements and recommendations made The illustrations are few but well selected the bibliography is good and the index is welcomed even though this is a small book All doctors in general practice internal medicine and surgery who manage cardiovascular diseases will find this to be a useful and practical book

ELECTRICAL IMPEDANCE PLETHYSMOGRAPHY The Electrical Resistive Measure of the Blood Pulse Volume Peripheral and Central Blood Flow ed 2 By Jan Nyboer D.Sc M D Springfield Ill 1970, Charles C Thomas Publisher 390 pages. Price $22 00

It has been approximately 10 years since Nyboer published the first edition of his book, *Electrical Impedance Plethysmography* The author is an expert on the subject, having devoted almost his entire professional life to this field This book summarizes and brings up to date his work and thinking on impedance plethysmography The book describes very well the principle of plethysmography and the applications of the impedance technique for measuring variations in blood flow with each heart beat. The original recording and illustrations are very good Nyboer has included drawings of the electric circuits used in his studies. The principles involved with the applications of impedance measurements are carefully and effectively presented The versatility and simplicity of the method is well known Nyboer shows how it can be applied to measuring blood flow in the limbs, fingertips, forehead and other parts of the body The method lends itself very nicely for studies of the effects of drugs and procedures in changing the rate of blood flow in selected parts of the body This is well exemplified by tracings obtained before and after the use of drugs and procedures. This is a good book which should prove to be useful to anyone interested in the peripheral circulation. It is recommended also for students and others who are involved with studying the cardiovascular system

CARDIOVASCULAR PATHOLOGY Vol 3 (Suppl. to Vols. I and 2) By Reginald E. B Hudson, M D F R C Path B Pharm. F.P.S. Baltimore 1970 The Williams & Wilkins Company 1 166 pages Price $71 75

This third volume is an excellent supplement to Hudson's first two volumes on cardiovascular pathology The field not only has been advancing rapidly but it has received relatively little attention so that a volume of this sort is needed. The material discussed not only included pathologic morphologic changes but normal morphology as well This is obviously necessary to appreciate fully the influence of disease Gross, histologic and ultrastructural changes are clearly defined for the heart conducting system arteries and veins. This volume is truly a supplement to the first two. Hudson integrates function clinical and even therapeutic principles, with the anatomic changes. This is done very well. It is unusual for example, to find a discussion of electric shock therapy for cardiac arrhythmias (p. S-118) in a book on morbid anatomy This may be considered unfortunate by some readers who are conventional pathologists. This, of course reflects the author's effort to make pathology of interest to the clinician. This may be so but this reviewer wonders if Hudson writes from experience with clinical cardiology The impression received from such sections of the book is that he writes from a review of the literature rather than from the point of view of a practicing cardiologist.

The presentation is excellent the illustrations good and the bibliography extensive. This volume and the previous two should be a part of the library of cardiologists and internists who practice a great deal of cardiology

HANDBUCH DER ALLGEMEINEN PATHOLOGIE, Herausgegeben von H W Altmann et al Die Organe, Die Organstruktur als Grundlage der Organleistung und Organerkrankung III Bearbeitet Von W Doerr H Otto, Redigiert Von H Meessen, and F Roulet Berlin Heidelberg New York, 1970 Springer Verlag, 821 pages. Price $85 00.

This volume on the pathology of diseases of the lungs and heart includes a rather extensive summary of modern techniques and concepts. For example, electron microscopic considerations are nicely presented The authors have attempted to describe a more dynamic approach to pathologic manifestations of the disease states than is

usually done in books of this nature. The illustrations are excellent nd reflect very well the pathogenesis of the diseases as ell the results t structural changes. The portion of the book devoted to the lungs represent about one third of the volume nd that related to the heart and blood vessels is included in the remainder The common diseases of the heart and l ngs are presented nd extensive bibliography is ppended t each section. This i very good olume of the series of handbooks on pathology

Books received

The History of C rdiac Surgery 1896-1955 By Stephen L. Johnson, Baltimore, 1970, Johns Hopkins Press, 201 pages. Price $9.50.

Knee Horizons. By M. Rocha Silva, American Lecture Series 781 *Springfield, Ill., 1970*, Charles C Thomas, Publisher 317 pages. Price $23 00.

Modern Treatment —March, 1970 Vol. 7 No. 2. 1. *Treatment of Pyelonephritis*, by John H Moyer and Charles D Swartz 2. Diuretics in the Management of Fluid Retention, by Henry O Heineman, New York, 1970, Harper & Row Publishers, 1,500 pages per year Price $20.00 per year

Pain and Suffering. By Benjamin L Crue, J *Springfield*, Ill 1970, Charles C Thomas, Publisher 205 pages. Price $12.75.

Physiolo an Pharmacology a Local Anesthesia. By Rudolph H. de Jong, M.D Springfield, Ill 1970 Charles C Thomas, Publisher 267 pages. Price $12.50.

Actualities de Physiologie Pathologique. By Jean-Louis Parrot with Francois Ri ff Paris, 1970, Masson & Cie 167 pages

Aspetti Istologici Enzimatici e Metabolici Delle Auricole di Soggetti Con Malattia di Bouillaud By A. Capurso Milano, 1969 *Recordati-Industria Chimica Farmaceutica*, S.A.S 123 pages.

Schock-und Kollaps-Fibel. By Ernst F Gersmeyer Erdem C. Y sargil, with W. W Hoep, W F Horstmann, and Rudolf Nissen, St ttgart, 1970, Georg Thieme Verlag 364 pages.

Corticosteroids in the Treatment of Shock. Edited by William Schumer nd Lloyd M. Nyhus, Chicago, Ill 1970, University of Illinois Press, 163 pages. Price $10.00.

Ergebnisse der Angiologie Band 2. By V Klukes Jahrestagung der Deutschen Gesellschaft fur Angiologie e.v om 6 Bis 8 June, 1968, *In Dusseldorf (President. Prof Dr E.* Derra) Stuttgart, 1969 F K. Schattauer 213 pages.

Food Values of Portions Commonly Used, ed. 11 By Charles Frederick Church, Philadelphia, 1970, J B Lippincott Company 180 pages. Price $5 40.

Mealtime Manual for the Aged and Ha di capped By Jud th La nefeld Klinger Fred H Frieden, and Richard A. Sullivan An Essandess Special Edition, New York, 1970, 242 pages. Price $2.00 paperback, and $5 95 hardcover

Book reviews

PERIPHERAL ARTERIAL DISEASE, A Physician's Approach. By Robert L. Richards, M D F R C P E D I R C P (Glasg) London 1970 E. & S. Livingstone Ltd 126 pages. Price $10 50

Richard has produced a very good and succinct discussion of peripheral arterial disease The approach is sound clinical and practical He describes the office and general hospital approach to the diagnosis and management of arterial disease of the limbs There are no frills, fancy and yet unevaluated procedures of diagnosis or treatment included He clearly defines what is useful in management of these diseases and the limitations in drugs and surgery The author in this brief book displays knowledge of the subject. This reviewer warns the readers that a profound knowledge of peripheral vascular physiology and clinical medicine will be required to appreciate the full implications of the statement and recommendations made. The illustrations are few but well selected the bibliography is good and the index is welcomed even though this is a small book All doctors in general practice internal medicine and surgery who manage cardiovascular diseases will find this to be a useful and practical book.

ELECTRICAL IMPEDANCE PLETHYSMOGRAPHY The Electrical Resistive Measure of the Blood Pulse Volume Peripheral and Central Blood Flow ed 2 By Jan Nyboer D Sc M D Springfield Ill 1970 Charles C Thomas Publisher 390 pages Price $22 00

It has been approximately 10 years since Nyboer published the first edition of his book *Electrical Impedance Plethysmography* The author is an expert on the subject having devoted almost his entire professional life to this field This book summarizes and brings up to date his work and thinking on impedance plethysmography The book describes very well the principle of plethysmography and the application of the impedance technique for measuring variations in blood flow with each heart beat. The original recording and illustrations are very good. Nyboer has included drawings of the electric circuits used in his studies. The principles involved with the applications of impedance measurements are carefully and effectively presented. The versatility and simplicity of the method is well known. Nyboer shows how it can be applied to measuring blood flow in the limbs, fingertips, forehead and other parts of the body The method lends itself very nicely for studies of the effects of drugs and procedures in changing the rate of blood flow in selected parts of the body This is well exemplified by tracings obtained before and after the use of drugs and procedures. This is a good book which should prove to be useful to anyone interested in the peripheral circulation It is recommended also for students and others who are involved with studying the cardiovascular system.

CARDIOVASCULAR PATHOLOGY Vol 3 (Suppl. to Vols. 1 and 2) By Reginald E. B Hudson M D F R.C Path B Pharm. F I .S Baltimore, 1970, The Williams & Wilkins Company 1 166 pages. Price $74 75

This third volume is an excellent supplement to Hudson's first two volumes on cardiovascular pathology The field not only has been advancing rapidly but it has received relatively little attention so that a volume of this sort is needed The material discussed not only included pathologic morphologic changes but normal morphology as well. This is obviously necessary to appreciate fully the influence of disease Gross histologic and ultrastructural changes are clearly defined for the heart conducting system arteries, and veins. This volume is truly a supplement to the first two Hudson integrates function, clinical and even therapeutic principles with the anatomic changes. This is done very well It is unusual for example, to find discussion of electric shock therapy for cardiac arrhythmias (p. S-118) in a book on morbid anatomy This may be considered unfortunate by some readers who are conventional pathologists. This, of course reflects the author's effort to make pathology of interest to the clinician. This may be so but this reviewer wonders if Hudson writes from experience with clinical cardiology The impression received from such sections of the book is that he writes from a review of the literature rather than from the point of view of a practicing cardiologist.

The presentation is excellent, the illustrations good and the bibliography extensive This volume and the previous two should be a part of the library of cardiologists and internists who practice a great deal of cardiology

HANDBUCH DER ALLGEMEINEN PATHOLOGIE, Herausgegeben von H W Altmann et al., Die Organe Die Organstruktur als Grundlage der Organleistung und Organerkrankung III Bearbeitet Von W Doerr H Otto, Redigiert Von H. Meessen and F Roulet Berlin Heidelberg New York, 1970 Springer Verlag, 8 1 pages. Price $85 00

This volume on the pathology of diseases of the lungs and heart includes a rather extensive summary of modern techniques and concepts. For example electron microscopic considerations are nicely presented The authors have attempted to describe a more dynamic approach to pathologic manifestations of the disease states than is

American Heart Journal

March 1971 Volume 81 Number 3

Editorial

Durability of prosthetic heart valves

John C Hylen Major MC USAF
USAF Academy Colo

The operative morbidity and mortality of surgical replacement of cardiac valves has decreased greatly in the past decade Therefore the long term follow-up and incidence of complications are of increasing importance in the search for better valves when replacement is necessary The incidence of postoperative complications is well documented for many prosthetic valves. These include thromboembolus hemolysis, sepsis, leak dislodgement thrombotic obstruction and the transvalvular gradient

In contrast, information concerning the in vivo durability of valvular prostheses is poorly documented for most valves. This is primarily because reliable statistics on the durability of valve replacement can be established only by reoperation or autopsy

The present report summarizes the problems related to silicone rubber poppets in prosthetic heart valves and emphasizes the necessity of better documentation of the durability of presently implanted materials

An increasing incidence of acute valvular malfunction and of death due to changes in the silicone poppets of cardiac valve prostheses has been noted. [3] These alterations include lipid infiltration with increased diameter grooving cracking decreased diameter fragmentation lipid lakes embolization of poppet material or thrombi and abnormal movement of the poppet due to sticking or cocking [3]

Aortic ball variance

Ball variance may be defined as mechanical dysfunction resulting from physical and chemical alterations in the Silastic poppets in cardiac valve prostheses. One of the frightening features of aortic ball variance is its frequent clinical silence until sudden catastrophe occurs.[1,2] Acute mechanical dysfunction of the Silastic poppets of aortic valve prostheses has been detected with the Models 1000 and 1200 Starr Edwards, Magovern sutureless SCDK-Cutter Harken ball valves, and with the Hufnagel disc valve.[1-4]

Information is available on the durability of the Model 1000 Starr Edwards aortic prosthesis. This valve is no longer in production but has been implanted in several thousand patients. Of the 47 long term survivors of aortic valve replacement performed between July 1 1963 and June 30 1964 at the University of Oregon Med

From the Department of the Air Force, USAF Academy Hospital, USAF Academy Colo.
The views expressed herein are those of the author and do not necessarily reflect the views of the United States Air Force or Department of Defense.
Reprint requests to Major John C. Hylen, Chief Cardiologist, USAF Academy Hospital, USAF Academy Colo. 80840

Announcements

THE CHICAGO HEART ASSOCIATION will present Nutrition in heart disease prevention and therapy—a practical workshop for physicians at the Sheraton Blackstone Hotel Chicago, Ill April 28 to 30 1971 For further information write to Jeremiah Stamler M D General Chairman c/o Chicago Heart Association 22 W Madison St. Chicago, Ill 60602

THE FOURTH INTERNATIONAL SYMPOSIUM ON DRUGS AFFECTING LIPID METABOLISM will be held in Philadelphia P from Sept 8 to 11 1971 The joint Scientific Secretaries are Dr William L. Holmes, Director Division of Research Lankenau Hospital Philadelphia and Professor Rodolfo Paoletti of the Institute of Pharmacology of the University of Milan.

The symposium has been divided into the following sessions Drugs affecting FFA mobilization Drugs affecting triglycerides Drugs affecting cholesterol and bile acid metabolism Drugs affecting serum lipoproteins Drugs affecting tissue lipids and obesity General

For further information and forms please contact Dr William L. Holmes, Scientific Secretary Symposium on Drugs Affecting Lipid Metabolism Lankenau Hospital Philadelphia Pa., 19151 (Tel. 215—M19-1400)

American Heart Journal

March, 1971 Volume 81 Number 3

Editorial

Durability of prosthetic heart valves

John C Hylen Major MC, USAF
USAF Academy Colo.

The operative morbidity and mortality of surgical replacement of cardiac valves has decreased greatly in the past decade. Therefore the long term follow-up and incidence of complications are of increasing importance in the search for better valves when replacement is necessary. The incidence of postoperative complications is well documented for many prosthetic valves. These include thromboembolus, hemolysis, sepsis, leak, dislodgement, thrombotic obstruction and the transvalvular gradient.

In contrast, information concerning the in vivo durability of valvular prostheses is poorly documented for most valves. This is primarily because reliable statistics on the durability of valve replacement can be established only by reoperation or autopsy.

The present report summarizes the problems related to silicone rubber poppets in prosthetic heart valves and emphasizes the necessity of better documentation of the durability of presently implanted materials.

An increasing incidence of acute valvular malfunction and of death due to changes in the silicone poppets of cardiac valve prostheses has been noted.[1,2] These alterations include lipid infiltration with increased diameter grooving, cracking decreased diameter fragmentation lipid lakes, embolization of poppet material or thrombi and abnormal movement of the poppet due to sticking or cocking.[1-3]

Aortic ball variance

Ball variance may be defined as mechanical dysfunction resulting from physical and chemical alterations in the Silastic poppets in cardiac valve prostheses. One of the frightening features of aortic ball variance is its frequent clinical silence until sudden catastrophe occurs.[1] Acute mechanical dysfunction of the Silastic poppets of aortic valve prostheses has been detected with the Models 1000 and 1200 Starr Edwards, Magovern sutureless SCDK-Cutter Harken ball valves and with the Hufnagel disc valve.[1-4]

Information is available on the durability of the Model 1000 Starr Edwards aortic prosthesis.[5] This valve is no longer in production but has been implanted in several thousand patients. Of the 47 long term survivors of aortic valve replacement performed between July 1 1963 and June 30 1964 at the University of Oregon Medi-

From the Department of the Air Force, USAF Academy Hospital, USAF Academy Colo.
The views expressed herein are those of the author and do not necessarily reflect the views of the United States Air Force or the Department of Defense.
Reprint requests to: Major John C. Hylen, Chief Cardiologist, USAF Academy Hospital, USAF Academy Colo. 80840

cal School 40 patients have been available for follow up Ball variance has been documented by autopsy or reoperation in 30 patients (75 per cent) Ball variance was noted at autopsy in 7 patients (18 per cent) and was considered the cause of death in 5 patients (13 per cent)[3] Patients unavailable for follow up lived in other states or countries or died without an autopsy

Absence of the aortic opening sound by auscultation is pathognomonic of ball variance and has been associated with marked changes in the phonocardiogram and sound spectrogram[3] In ball variance the phonocardiogram shows a decrease in the intensity of the aortic opening sound as compared with the aortic closure sound These findings have been noted with the Starr Edwards Magovern sutureless and SCDK Cutter aortic valves[1 6]

The aortic opening sound is usually less than half the intensity of the aortic closure sound (AO/AC less than 0 5) in patients with variant poppets with the equipment previously reported[3 4] However the word of caution regarding these standards has not been heeded The range of normal and abnormal of the AO/AC ratio must be standardized for each individual phonocardiograph Some authors have used the range of AO/AC less than 0 5 without standardization[7 8] and one author has suggested these standards for another prosthesis[9]

Patients with ball variance have been known to have an aortic opening sound of lower frequency (a thud rather than a click) than is usually found with the Starr Edwards aortic prosthesis Changes in the frequency of the aortic opening sound have been noted by auscultation and phonocardiography but cannot be quantitated by these techniques. The loss of the high frequency components of the aortic opening sound is a characteristic finding of ball variance by sound spectrography[3 10] This suggests that the use of phonocardiographic equipment recording high frequency sound (greater than 1 000 Hz) should be more specific for the diagnosis of ball variance than previously reported.[3 4]

Although embolic complications of aortic ball variance have been previously noted the correlation of late emboli with ball variance is not generally appreciated An increased incidence of late thromboembolic complications has been observed in both aortic and mitral ball variance[1,2]

Cracking or lipid lakes within the poppet may be detected by radiographs in those patients who have barium impregnated silicone poppets.[3 11] The late onset of aortic regurgitation or severe hemolysis with anemia is frequently associated with ball variance[1,2 3 5 16]

The symptoms of ball variance are non specific and include fatigue dyspnea on exertion palpitation dizzy spells, angina and syncopal episodes The diagnosis of aortic ball variance is based on the absence of the aortic opening sound a consistently abnormal phonocardiogram or sound spectrogram or both recurrent embolic episodes late onset of aortic regurgitation or hemolysis or both or radiographic evidence of an abnormal barium impregnated poppet[3]

The diagnosis of aortic ball variance remains difficult because most of the symptoms and signs of the syndrome are non specific and many patients are asymptomatic. Complete absence of the aortic opening sound which is pathognomonic for aortic ball variance occurred in only 25 per cent of our patients.[3] A persistently abnormal sound spectrogram occurred in 78 per cent of those studied preoperatively and is the most consistent finding of ball variance.[3]

A high incidence of sudden episodes of severe angina syncope and hypotension have been noted in cases of SCDK Cutter aortic ball variance before death[3] In the face of the above findings and an absence or decrease in the aortic opening sound urgent surgical correction should be undertaken If myocardial infarction has occurred the decision for reoperation is more difficult However the prognosis without surgical intervention is poor[4]

Patients having aortic valves with silicone rubber poppets should be examined at six month intervals. Careful auscultation with particular attention to the quality of the aortic opening sound and a phonocardiogram should be recorded Patients developing findings of aortic ball variance should be reoperated upon if their general medical condition warrants it.

Mitral ball variance

Valve dysfunction due to changes in the silicone rubber ball have been noted in the Model 6000 Starr Edwards and SCDK Cutter mitral ball valves.[3,4] Four cases of mitral ball variance in Starr Edwards valves have been reported to the manufacturer.

Fifteen cases of SCDK-Cutter mitral ball variance have been reported.[3,9,21,22] The SCDK-Cutter mitral valves are particularly vulnerable to problems of lipid absorption and poppet swelling. Clearance of 0.003 to 0.005 inch is allowed between the poppet and the annulus to avert excessive regurgitation. This means that swelling of 0.006 inch causes sticking in all SCDK-Cutter mitral valves. Therefore a small increase in the diameter of the ball due to swelling, which would be of little or no significance in the Starr Edwards prosthesis, can produce serious valve dysfunction because the ball can impact in the inflow orifice.[3,23,24]

The symptoms associated with mitral ball variance are fatigue, hemoptysis, chest pain, dyspnea, orthopnea, ankle swelling, palpitation, syncopal episodes, and dizzy spells. The patient with mitral ball dysfunction, in contrast to aortic ball variance, is usually symptomatic and has signs of congestive heart failure.

The typical physical findings are fluctuating pulse volume, varying intensity of the mitral closing sound, intermittent opening click, and a variable duration of the second sound to opening click interval.[21,22] With SCDK Cutter mitral ball variance the diagnosis may be confirmed by the phonocardiographic findings of an intermittent opening click, a varying interval between the aortic closing and mitral opening sounds, and a varying intensity of the mitral closing sound. Elevated left atrial pressure varying from beat to beat may be found at catheterization and is due to the ball valve only opening intermittently.[21,22]

The decrease or absence of prosthetic sounds or varying interval between the aortic closing sound to mitral opening click is not diagnostic of poppet deterioration because these findings are also noted in thrombotic obstruction.[25] However surgical intervention is indicated whatever the etiology of the mechanical dysfunction.

Patients with mitral ball valves with silicone rubber poppets should be examined at six month intervals. This is particularly important with patients having SCDK Cutter valves. Careful auscultation and phonocardiogram should be recorded with particular attention to variation in the intensity of prosthetic sounds and the duration of the interval between the aortic closing sound and mitral opening click. Patients with the findings of mitral ball variance should be scheduled for reoperation. If the diagnosis remains uncertain, cardiac catheterization should be undertaken to rule out mechanical dysfunction.

Disc cocking

Since the introduction of the low profile prosthetic heart valve in 1965, several new low profile disc valves have been designed. Concern for the ultimate longevity of these low profile valves is based on both in vitro and in vivo data.

In general, lens wear is more rapid and less evenly distributed than ball wear under comparable stress situations. A lens tends to rotate less and strikes the frame harder during each cycle.[14] When opening or closing, the disc frequently does not stay perpendicular to the central axis.[1] This increases the stress on the edge of the disc and the strut. Wearing of the disc or struts has been noted depending on which is the harder material.

Abnormalities in the discs of mitral valves have been detected in the Hufnagel,[1,11,26] Kay Shiley,[1,26,27] Kay-Suzuki,[1,28] Cross-Jones,[1] and Beall valves. Cocking of the disc may be defined as tilting of the disc in a fixed position. Three reported cases of mitral disc cocking have developed acute mitral regurgitation, pulmonary edema, and hypotension. Prosthetic valve sounds were absent and a loud systolic murmur was heard. There were no survivors.[19,27,28] In patients with disc valves, the onset of intermittent pulmonary edema or congestive heart failure strongly suggests cocking of the disc.

Intermittent cocking of the disc has been noted in the early postoperative period with the Cross-Jones prosthesis and is usually associated with aortic regurgitation.[29,30] However, the late onset of inter

cal School 40 patients have been available for follow up Ball variance has been documented by autopsy or reoperation in 30 patients (75 per cent) Ball variance was noted at autopsy in 7 patients (18 per cent) and was considered the cause of death in 5 patients (13 per cent) [2] Patients unavailable for follow up lived in other states or countries or died without an autopsy

Absence of the aortic opening sound by auscultation is pathognomonic of ball variance and has been associated with marked changes in the phonocardiogram and sound spectrogram [2] In ball variance the phonocardiogram shows a decrease in the intensity of the aortic opening sound as compared with the aortic closure sound These findings have been noted with the Starr Edwards Magovern sutureless and SCDK Cutter aortic valves [1-6]

The aortic opening sound is usually less than half the intensity of the aortic closure sound (AO/AC less than 0 5) in patients with variant poppets with the equipment previously reported [2,6] However the word of caution regarding these standards has not been heeded The range of normal and abnormal of the AO/AC ratio must be standardized for each individual phonocardiograph Some authors have used the range of AO/AC less than 0 5 without standardization [7,8] and one author has suggested these standards for another prosthesis [9]

Patients with ball variance have been known to have an aortic opening sound of lower frequency (a thud rather than a click) than is usually found with the Starr Edwards aortic prosthesis. Changes in the frequency of the aortic opening sound have been noted by auscultation and phonocardiography but cannot be quantitated by these techniques. The loss of the high frequency components of the aortic opening sound is a characteristic finding of ball variance by sound spectrography [2,10] This suggests that the use of phonocardiographic equipment recording high frequency sound (greater than 1 000 Hz) should be more specific for the diagnosis of ball variance than previously reported [2,6]

Although embolic complications of aortic ball variance have been previ

preciated An increased incidence of late thromboembolic complications has been observed in both aortic and mitral ball variance [2,3]

Cracking or lipid lakes within the poppet may be detected by radiographs in those patients who have barium impregnated silicone poppets [2,11] The late onset of aortic regurgitation or severe hemolysis with anemia is frequently associated with ball variance [1,2,4,5,10]

The symptoms of ball variance are non specific and include fatigue dyspnea on exertion palpitation dizzy spells, angina and syncopal episodes. The diagnosis of aortic ball variance is based on the absence of the aortic opening sound a consistently abnormal phonocardiogram or sound spectrogram or both recurrent embolic episodes late onset of aortic regurgitation or hemolysis or both or radiographic evidence of an abnormal barium impregnated poppet [2]

The diagnosis of aortic ball variance remains difficult because most of the symptoms and signs of the syndrome are non specific and many patients are asymptomatic Complete absence of the aortic opening sound which is pathognomonic for aortic ball variance occurred in only 25 per cent of our patients.[2] A persistently abnormal sound spectrogram occurred in 78 per cent of those studied preoperatively and is the most consistent finding of ball variance [2]

A high incidence of sudden episodes of severe angina syncope and hypotension have been noted in cases of SCDK Cutter aortic ball variance before death [4] In the face of the above findings and an absence or decrease in the aortic opening sound urgent surgical correction should be undertaken If myocardial infarction has occurred the decision for reoperation is more difficult However the prognosis without surgical intervention is poor [2]

Patients having aortic valves with silicone rubber poppets should be examined at six month intervals. Careful auscultation with particular attention to the quality of the aortic opening sound and a phonocardiogram should be recorded Patients developing findings of aortic ball variance should be reoperated upon if their general

cator of ball variance of aortic valve prosthesis, Circulation 40:55, 1969
9. Technical Bulletin. Cutter Laboratories, Inc., California, 1969
10. Hylen, J. C., Kloster F. E., Herr R. H., Starr A., and Griswold, H. E.: Sound spectrographic diagnosis of aortic ball variance, Circulation 39:849 1969
11. Hylen, J. C., Judkins, M. P. Herr R. H., and Starr A. Radiographic diagnosis of aortic ball variance, J.A.M.A. 207 1120, 1969
12. Sanderson, R. C. Hall, A. D and Thomas, A. N Clinical diagnosis of ball variance in mitral valve prosthesis, Ann. Thorac. Surg. 6:473 1968.
13. Lee, S. J. K., Zaragoza, A. J. Callaghan, J. C., Couves, C. M., and Sterns, L. P. Malfunction of the mitral valve prosthesis (Cutter Smeloff) clinical and hemodynamic observations in three cases, Circulation 42:479 1970.
14. Braunwald, N. S., and Detmer D. E.: Critical analysis of the status of prosthetic valves and homografts, Progr Cardiovasc. Dis. 11 113, 1968.
15. Craige, E., Hutchin, P and Sutton, R. Impaired function of cloth-covered Starr Edwards mitral valve prosthesis. detection by phonocardiography Circulation 41 141, 1970.
16. Cheng, T. O., Kinhal, V and Tice, D. A. F tal thrombosis of the Starr-Edwards mitral valve prosthesis associated with bacterial endocarditis, Dis. Chest 57:151, 1970.
17. Spencer F. C., Trinkle, J. K., and Reeves, J. T Successful replacement of thrombosed mitral ball-valve prosthesis, J.A.M.A. 191:1249 1965.
18. Roberts, W. C., and Morrow A. G. F tal degeneration of the silicone rubber ball of the Starr Edwards prosthetic aortic valve, Amer J Cardiol. 22:614, 1968.
19. Vaskin, J. S., and Leighton, R. F Acute massive mitral regurgitation resulting from disc-valve malfunction, Ann. Thorac. Surg. 6:564, 1968.
20. Carey J. S., and Hughes, R. K. Complication of mitral-valve replacement with caged-lens prosthesis, Ann. Thorac. Surg. 6 77 1968.
21. Vogel, J. H. K., Paton, B. C., Overy H. R., and Blount, S. G. Abnormal hemodynamic function after disc mitral valve replacement, Circulation Suppl. I 141, 1969
22. Low H. B. C., and Lefemine, A. A.: Acute mitral insufficiency due to jamming of a disc-valve prosthesis, Ann. Thorac. Surg. 4 71 1967
23. Edgett, J. W., Nelson, W. P. Hall, F. J., Jahnke, E. J and Aaby G. V.. A complication of valve replacement by a caged-lens prosthesis, Circulation 36:122, 1967
24. Hammermeister K. E., Dillard, D. H., and Kennedy J. W.: Severe, intermittent, mitral regurgitation in Cross-Jones valve, J Thorac. Cardiovasc. Surg. 58:575 1969
25. Horsley H. T Rappoport, W. J Vigoda, P. S., and Vogel, J. H. K.: F tal malfunction of Edwards low profile mitral valves, Circulation 40 (Suppl. III) 109 1969
26. Magovern, G. J Begg, F. J Kent, E. M Cushing, W. B., Gerber M. L., and Fisher D. L. The experimental and clinical results of modified cage disc mitral prosthesis, J Thorac. Cardiovasc. Surg 59 109 1970.
27. Cross, F. S., Akao, M and Jones, R. D.: The evaluation of experimental mitral valve prostheses in the dog, Surgery 65:89 1969
28. Gonzalez-Crussi, F Mandy S., Johnson, J. E., and Green, J. R.: Teflon embolism of coronary arteries J Thorac. Cardiovasc. Surg. 51:53, 1967
29. Aquino, T. I and Skinner, O. K.: Teflon embolism of coronary arteries, Arch. Path. 80:625 1965
30. Bjork, V. O Cullhed, I., and Lodin, H.: Aortic valve prosthesis (Teflon). Two-year follow-up, J Thorac. Cardiovasc. Surg. 45:635, 1963.
31. Edmark, K. W Hill, W. J., Thomas, G. I and Jones, T. W.: A central-flow low-profile, leaflet deforming mitral valve prosthesis free of prolonged anticoagulation requirements, J Thorac. Cardiovasc. Surg. 58:713, 1969
32. Reis, R. L., Glancy D. L., O'Brien, K., Epstein, S. E., and Morrow A. G.: Clinical and hemodynamic assessments of fabric-covered Starr Edwards prosthetic valves, J Thorac. Cardiovasc. Surg. 59:84, 1970.
33. Spencer F. C., Reed, G. E., Clauss, R. H., Tice, D. A., and Rappert, E. H. Cloth-covered aortic and mitral valv prostheses: Experience with 113 patients, J Thorac. Cardiovasc. Surg. 59:92, 1970.

mittent jamming should be considered a precursor of permanent malfunction[19,21,22] and surgical intervention is indicated

A syndrome similar to thrombotic obstruction with ball valves has been noted with disc valves. Thrombus formation or pannus on the strut prevents normal movement of the poppet and closing of the valve[1,21,23] Associated grooving of the disc has been described[1,21] Although found in all presently used disc valves the syndrome is particularly prevalent in the Model 6500 Starr Edwards valve[23] Symptoms and signs of restenosis and insufficiency are usually present Decreased poppet excursion is noted by fluoroscopy Urgent reoperation is indicated to prevent a lethal outcome[23]

Patients with disc mitral valves should be examined at six month intervals Careful auscultation with particular attention to the quality of the prosthetic sounds should be noted A phonocardiogram should also be recorded Patients with altered prosthetic sounds congestive heart failure either intermittent or chronic arrhythmia or symptoms suggesting possible disc malfunction should have fluoroscopic and cineradiographic examinations to determine if decreased poppet motion or intermittent cocking is present Patients with intermittent jamming of the disc should be reoperated upon to prevent the high mortality rate seen in those cases with permanent cocking of the disc[19,21,22]

Conclusion

Lipid infiltration causes loss of the polymerized structure of the silicone rubber with decreased elasticity and structural strength Therefore an increased incidence of acute valvular dysfunction of all prostheses utilizing silicone rubber poppets should be anticipated

Antemortem diagnostic techniques should be evaluated by those medical centers using such valves. Since standardized phonocardiographic and special radiographic techniques are required in patient follow up the large medical centers which replace valves should undertake follow up examinations. The family physician should be alerted to possible symptoms or signs of mechanical dysfunction so that rapid referral to such centers can be accomplished

In one series, 11 of 12 (92 per cent) deaths in those patients who survived more tha two years after aortic valve replacemen were caused by ball variance.[1,16] The ab sence of aortic ball variance at some medica centers must be assumed to be due to low autopsy rate.[1]

Although this report is primarily con cerned with the longevity of silicone rubber the durability of Teflon[1,16-18] polypropy lene[1,17,21] polycarbonate[1,16] titanium al loys[1,17,21,22] and cloth coverings[1,16,17,21,2] has also been questioned The recent trenc to harder poppet material such as Teflon may delay poppet destruction however adequate durability must be demonstrated in vivo

Since the lives of many thousands of patients are already in possible jeopardy because of the unknown longevity of replaced valves (prosthetic or otherwise) an accurate in vivo assessment of the presently used materials is indicated Unless autopsy and examination at reoperation are performed with increasing frequency the durability of many valves will remain uncertain Delay in the documentation of a superior valve for replacement will involve the lives of many thousands of patients yet to be operated

RFFERENCES

1 Brewer L. A. Prosthetic heart valves, Springfield Ill. 1969 Charles C Thomas, Publisher
2. Hylen J C Kloster F E. Starr A. and Griswold H E. Aortic ball variance diagnosis and treatment, Ann. Intern. Med 72:1 1970.
3 McHenry M M Smeloff E. A. Fong, W Y Miller G E. and Ryan, P M Critical obstruction of prosthetic heart valves due to lipid absorption by Silastic, J Thorac. Cardiovasc. Surg 59 413 1970.
4 Bircks, W and Loogen F Phasische funktionsverschlechterungen eines aortenklappenventils durch balldeformierung Deutsch Med. Wschr 93:803 1968.
5 Otto, T J Cleland W P and Bentall H H Results of aortic valve replacement with Starr Edwards prosthesis, J Cardiovasc. Surg 10:339 1969
6 Hylen J C. Kloster F E. Herr R. H Hull P Q Ames, A. W Starr A. and Griswold H E.: Phonocardiographic diagnosis of aortic ball variance Circulation 38:90, 1968.
7 Delman, A. Tal, A. Shah A. and Robinson G: Phonocardiographic and hemodynamic correlates of simulated aortic ball variance Circulation 40 (Suppl. III):68, 1969
8. Miller B L. Pearson, H. A. Wheat, M W White, A. W and Schiebler G. L.: Delayed onset of hemolytic anemia in a child an indi-

This pilot study of the incredible degrees of physical stamina habitually developed by the Tarahumara Indians is offered on the precept that often valuable clues can be gleaned from observations of extremes—of use of medications (e.g. determination of the "minimum lethal dose") or alcohol, of stresses, aggression, slothfulness, or dietary excesses, as of many physiologic variables. In the same way, we might look for the limiting factors in human physical endurance, a sort of M.L.D. of exertion, and for its ultimate effects on the heart which must inevitably sustain the brunt of that exertion.

The Tarahumara and their feats

Little is known of the origins of the Tarahumara, though they are classed by anthropologists as one of the few Uto-Aztecan tribes to survive as functioning aboriginal cultures, largely sequestered from civilization and retaining many of their prehistoric modes of life. Presumably they were found there by the early Spanish settlers who came into the Sierra Madre Occidentale Mountains of Mexico in the sixteenth century. Advancing civilization has rolled back their lands which now are confined largely to the southern third of the state of Chihuahua and range in topography from tropical gorges as much as a mile deep to the vast rocky and wooded highlands, little of which is tillable. Further isolated by their language, which is unwritten and unique, the Tarahumara are a shy people who still mix little with the more familiar Mexican cultures and continue to subsist, dress, eat, and play much as they did as long ago, perhaps, as the heyday of the Spartans.

Staple of their diet is pinole, a highly concentrated food made from finely ground, toasted corn, eaten in many forms, liquid and solid.[4] Even their mainstay intoxicant tesguino is a fermentation product of corn sprouts. Various preparations of beans furnish a large part of the protein in the diet, while squash and assorted greens supply much of the bulk. In times of corn shortage, wheat is used extensively, and in very lean months, numerous wild plants and roots are resorted to, including cactus. Several fruits are cultivated, as is strong tobacco which the Tarahumara smoke in cornhusk cigarettes. Relatively little meat is consumed and seldom is livestock slaughtered for food except on occasions of fiestas and tesguinadas (which evidently are not infrequent). Undernutrition and malnutrition are known to be widespread.

Unusual stamina has characterized the Tarahumara from the earliest recorded descriptions of the tribe. As would be expected, anthropologists long preceded physicians in investigative sorties into this remote area. Amazing physical feats are described by the explorer Lumholtz, who lived among these people in the 1890's and provided a detailed account not only of their foot races but of their entire culture. A more modern compilation of virtually all the anthropological literature to date, as well as their own first-hand observations of these Indians, is the excellent book by Bennett and Zingg, which likewise documents the rigorous Tarahumara existence and such feats as what must certainly be the most primitive method of hunting a deer, that of running after him relentlessly for a couple of days until the animal drops from exhaustion. Similarly the wild turkey is stalked simply by pursuing him until he can no longer rise from the ground in flight. And other game ranging in size from birds and mice up to coyotes are commonly felled by rocks which the hungry hunters learn to throw with uncanny accuracy. Ingeniously these Indians have learned to harvest fish by introducing into the water upstream drugs* which stupefy the fish, rendering them literally "doped" to the gills, yet still fit for the Tarahumara table. A veritable pharmacology of fishing and of ceremonial drugs, data on their diet, along with an exhaustive bibliography dating back to Jesuit records of 1645, are included in the monograph of Pennington.

In a region with no roads and many paths, some of them negotiated more readily on foot than by burro, running affords a very real utility as well as sport. Tarahumara are said to compete effectively with mules as a means of transportation because they go faster and further in a day, carrying heavy loads of mining timbers and lumber for hours at a time up and down steep mountain slopes. With their unmistakable

*Prepared chiefly, according to Pennington, from *Cassia decompositum*, *Croton ladysi*, *Coriolanus edulis*, and *C. pubida*.

Clinical communication

Cardiovascular observations on Tarahumara Indian runners—the modern Spartans*

Dale Groom M D F A C P
Oklahoma City Okla

Cardiologists have become increasingly interested the last few years in the effects of physical conditioning on the cardiovascular system The thought has been that in general our present-day civilization (whose benefits we certainly do not decry) may be leading us into a more and more sedentary type of life to the detriment of certain basic adaptive mechanisms including those regulating function of the heart Moreover it has been contended largely on clinical grounds that we might beneficially utilize various regimens of deliberate physical conditioning to forestall the ravages of ischemic heart disease or even to improve the prognosis once that disease has become manifest

Life has of course not always gone on so comfortably for *Homo sapiens* What aeons of our primordial ancestors did with their stones and clubs and caves we can only surmise But we do have in recorded history a high state of physical culture and development achieved by the ancient Spartans who it will be recalled took children from their parents at an early age for years of intensive training in physical feats now legendary That their incentive was survival itself (in the more or less constant combat which they waged with the Athenians for several centuries B C.) doubtless accounted in large part for the Spartan constitution Theirs was perhaps history s most illustrious chapter of physical attainments and prowess before the human brain supplanted muscle as man s dominant means of conquest of his environment and of his fellow man

A modern counterpart of the Spartans is found in a little known tribe of Indians, variously estimated to number from 30 000 to 50 000 residing in an isolated area of mountains encompassing the continental divide of northern Mexico Their name Tarahumara probably a corruption of Raramuri liberally translated from their language means fleet foot or foot runner and their habitat for perhaps 2 000 years has been in and around the great Barranca del Cobre far off the tourist beat Rather than war the incentive for physical development among the peace-loving Tarahumara doubtless lies in the stark reality of sustaining existence in some of the most rugged and craggy wilderness of North America Probably even more of an inducement however is the fact that running is the principal sport Being fleet of foot is at the same time his livelihood his recreation and his criterion of success

From the Department of Medicine University of Oklahoma School of Medicine, Oklahoma City Okla.
Received for publication April 20, 1970.
Reprint requests to: Dr Dale Groom, University of Oklahoma Medical Center 800 Northeast Thirteenth St., Oklahoma City Okla. 73104.
*Presented in part at the Fiftieth Annual Session of the American College of Physicians, Chicago, Ill April 23 1969

March 1971 Vol 81 No 3 pp 304 314



Fig. 1. Tarahumara running barefoot through meadow near the Mission with the kickball in air (arrow). Native men are clad in a loincloth attire which is ideally suited to long swinging stride. Women, on the other hand, manage somehow to run dozens of miles in almost ankle-length, colorful skirts, even with a papoose on the back.

runners at a small mission hospital in Norogachi about fifty miles to the south of that, not far from the spectacular Barranca del Cobre.

For purposes of these studies, a Tarahumara kickball race was staged (at the behest of their beloved padre, Father Llaguno and with the substitution of a few pesos and articles of clothing for the native wagers) from Sisoguichi to Panalache and return. The measured distance of this course was 23 km. each way or a total of 28.6 miles. This mileage, it should be noted is that of the over-all course distance, whereas the actual distance traveled by the runners in their devious pursuit of the balls, up and down over rugged terrain at altitudes of 7,000 to 8,000 ft. above sea level was lengthened by an appreciable but unmeasurable amount. Eight male Indian runners ranging in age from 18 to 48 yr competed in two teams of four each, the winners covering this course in four hours fifty five minutes running time, the others crossing the finish line approximately fifteen minutes later. Calculated average speed of the winning team was 5.81 miles per hour. Since no allowance was made for time lost or digressions along the way looking for lost balls or for the requirement of having pieces of paper signed by the Mayor of Panalache at the turnaround point on the course, their actual running speed would average over six miles per hour* for the race. Observations of pulse rate and blood pressure were made before, during (at a three-quarter point which we reached by jeep travel) and at the end of the race. All runners finished easily what was obviously regarded by them as little more than child's play.

Summarizing the data, each contestant in the race lost about five pounds in weight, attributable to dehydration at that ambient temperature of approximately 65° F. More surprising was the marked decrease in diastolic blood pressure which was a universal finding. Whereas all the runners had normal blood pressures at the beginning, two of them (ages 22 and 32) showed diastolic readings of zero during and immediately at the end of the race, rising within a few minutes to 60 to 80 mm. Hg. Others had diastolic levels (by the usual cuff method) ranging from 40 down to 8 mm. Hg. All runners, checked both at the three-quarter point and at the end of the

*Again I should emphasize that this is not a *fast* race on standards of, say, the Boston Marathon. It is the *endurance* of the Tarahumara runners that is unique, demonstrated in races over courses several times that distance.

native attire they are a familiar sight in the city of Chihuahua capitol of their state some of them traveling afoot hundreds of miles en route

But the Tarahumara's high level of physical conditioning is nowhere as evident as in his kickball races which seem to constitute almost the *raison d'etre* of a harsh and precarious existence Documentation of these marathons is abundant[1-4] The sport consists of running continuously day and night along paths and trails over mountainous terrain kicking (actually *flicking with the dorsum of the foot*) a ball the size of a tennis ball carved from wood with a machete knife Races covering linear distances of 75 miles or so are common while major inter pueblo races go on for as long as two days and two nights covering in a monitored number of laps over a marked course as much as 150 miles and more If a runner drops out for pinole or for curing of his legs or other ministrations by his medicine man he must make up the lost distance upon rejoining his team before he is again eligible to kick the ball Betting is the order of the day on these festive occasions clothes livestock jewelry knives blankets even land are wagered in days or weeks of ritualistic preparations by villagers as many as several hundred of whom then join in the competition by running along a lap or two spurring on their teams or trying to confound their opponents, carrying torches at night or supplying small rations of food and fluids to the contestants as they pass by A recent race near Sisoguichi witnessed by the local padre Father Llaguno covered a measured distance of 161 miles, only two of the twelve entrants finishing Interestingly a traditional prize of victory is said to be a special popularity with the women (although how much of a reward that would actually prove to be for a man who had been running for two days and a night is questionable to say the least!) Therein may lie some element of natural selection

Certainly such fantastic feats of endurance can be achieved only after long arduous and perhaps unprecedented physical conditioning The Tarahumara begins running almost as soon as he learns to walk[3] Groups of small children are frequently seen racing along trails and over hills pursuing their kickballs. More or less practice races of fifty miles or so are a favorite pastime among members of the same community and even a solo traveler through the countryside may be seen jogging along behind his kickball which he learns to propel with unerring control Women of the tribe have their own type of race employing small hoops which they hurl through the air with sticks. Their contests extend over shorter distances although they also last through the night and entail much wagering[1,2] It should be emphasized that the Tarahumara excels not in speed but in endurance His gait is a rhythmic swinging one (Fig 1) that bespeaks an economy of effort his pace is moderate but unrelenting

Physical and physiologic observations

Detailed investigation of runners in action poses certain problems. One is that the really big races are unscheduled and unpredictable as to time and place More important to the Tarahumara a kickball race is serious business, for not only does it rate him as a man but it entails betting what to him may be high stakes. Understandably he does not want to be encumbered by monitoring devices or detained by unfamiliar examination procedures. Then too the competition (as well as practically all spheres of Tarahumara life) is fraught with much mysticism and superstition which can impart fearful significance to even commonplace occurrences. More trusting and tolerant of strange gadgetry such as stethoscopes and electrocardiographs are those Indians who have lived in or around one of the mission settlements established by the Jesuits two and three centuries ago They are undoubtedly less primitive than their more isolated tribesmen whose lives have not been touched by the Caucasian influence of the missions or lumber camps but first hand observation attests to their quaint native ways and their marvelous feats of physical endurance Headquarters for these studies was the mission at Sisoguichi lying 100 miles southwest of the capitol city of Chihuahua while the chest x rays were made on other Tarahumara

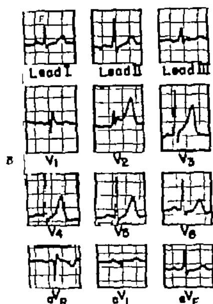


Fig. 3B ECG on 44-year-old Louis Diaz recorded 15 min after the race. It does not differ significantly from that of the "control" subject (3 C).

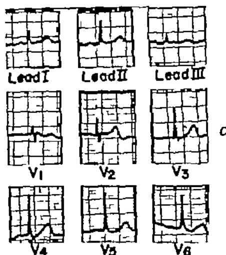


Fig. 3C. ECG on 38-year-old Nikolas, the "control" Tarahumara, who spent his years in the less strenuous life of the Mission.

Certain physical characteristics of these runners are worthy of note. Those competing in the Sisoguichi Panalache race were conspicuously thin and relatively short as compared with United States population standards. In height they measured from 5 ft. 2 in. to 5 ft. 6 in. and the average weight was 120 lb. (range 114 to 135 lb.). An idea of the leanness of these people is conveyed in the measurements which we made of the abdominal panniculus by caliper: in all eight of our runners a single fold of fat pad was less than one centimeter, most of them only 5 to 7 mm. (The two United States examiners must blushingly admit to measurements nearly ten times as great.) As a Tarahumara control, our houseboy and jeep driver, Nikolas, who had been born and raised amid the comparative comforts of the Mission, had an abdominal panniculus of 3.5 cm., was 5 ft. 4 in. in height, weighed 134 lb., had a resting blood pressure of 95/60, pulse 72, and the normal electrocardiogram shown in Fig. 3 C.

All eight of the contestants in the race were examined carefully and none were found on physical examination to have evidence of cardiac enlargement, unusual accentuation or splitting of the second heart sound, or suspicious murmurs. Their musculature was impressively firm. Almost unbelievable is the pulmonary performance of these runners who, after running competitively for hours, cross the finish line and stand quietly without panting while one examines them, seemingly unperturbed by the effort. At the conclusion they show a calmness not evident in the anticipation of the race.

Discussion

What then are the limiting factors at the extreme end of the scale of human physical endurance? Really definitive physiologic data are exceedingly difficult to come by in these isolated, clannish people who speak an unwritten language of their own and are not even counted on the country's census with any degree of accuracy. Meaningful medical records or just simple vital statistics are virtually unknown in the Tarahumara, for relatively few of them are ever seen by a nurse, fewer yet by a physician. Most still live and die much in their ancient patterns which are not readily amenable to scientific scrutiny. Thus an investigator of their ways is left with the limited literature available, mostly anthropological, with whatever first-hand observations of these people he can muster, and with the few interpretive bridges to their culture, such as Father Llaguno and acculturated Indians

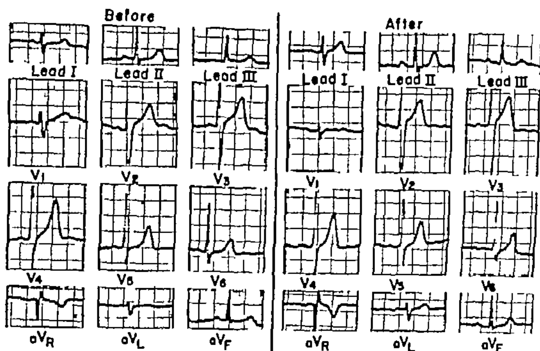


Fig 2 Electrocardiogram before and immediately after the 28 mile race recorded (supine) on 23-year-old Severiano Saldo one of the winning team

race showed declines of systolic as well as diastolic pressures the highest levels being 122/80 and the average approximately 110/70

Pulse rates were determined as were all the blood pressures within a minute or two and with the subjects standing The maximum rate recorded was 158 beats per minute that in the latter half of the race and on the 23 year-old runner whose electrocardiogram is illustrated in Fig 2 (ECGs of two of the other contestants are shown in Fig 3 along with that of a thoroughly acculturated control) Rates on all the others were in the 120 to 150 range counted immediately after crossing the finish line True resting pulse rates as with the blood pressures were not obtainable in the aura of excitement with anticipation of the contest and the unfamiliar medical preparations which we introduced but they ranged here from 62 to 90 standing (Subsequent counts on four adult runners checked supine and without the competitive stimulus of a race disclosed rates of 56 to 60) All these observations are in line with those of Balke and Snow[4] who in a similarly staged Tarahumara race also found increases in serum cholesterol levels of about 25 per cent above the pre-race values which incidentally were generally below

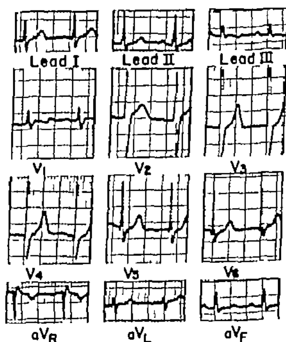


Fig 3 1 Electrocardiogram (ECG) on 22 year-old Francisco R z taken at the end of the race

100 mg per 100 c c The mean hemoglobin levels (17 2 Gm) and hematocrits (51) which they reported are explainable on the mile and one-half high elevation of this area of Mexico

comfort, but never any pain in the chest, arms, shoulders, or neck. Nor could anyone recall over the years a specific instance of a contestant dying during a race. However rare cases of death after unusually long races were acknowledged with time intervals presumably of no more than a few days.

A common type of complaint had to do with disturbances in urination. Apparently runners become especially concerned over any scanty urination or anuria occurring either during or after long races. It is understandable that dehydration accompanying the exertion would cause an oliguria, but evidently a reduction or absence of urine output may occasionally persist for several days in some of the more discomforted participants. One wonders whether acute renal failure might be a reversible consequence in these circumstances, resulting perhaps from hemoglobinuria or myoglobinuria. Usually though the contestants, after an especially long marathon will indulge themselves in much rest and food for a week or so, then rise to race another day

Unquestionably the main physical factor which limits endurance in Tarahumara races is that of pains in the legs. From all the accounts, these are predominantly muscle rather than joint pains and they are of such import to the runners that literally days are spent before and after major events in ritualistic bathing or "curing" of the legs, anointing them with various nostrums such as herbs and goat grease. Despite all this apparently it is skeletal muscle which gives rise to most of the symptoms associated with the longer races and claims the greatest number of physical casualties. Really outstanding contenders are said to become so imbued with the spirit of the competition that they are insensitive to all pain until later Losers, on the other hand, fall by the wayside either because they are bewitched by one of the many bizarre (and ostensibly potent) superstitions* of racing or because their threshold for discomfort or fatigue is lower Runners made of sterner stuff go on to victory and the rewards of their wagers and their laurels.

*For example, one insidious "hex" perpetrated by the shaman (medicine man) of [illegible] team is to exhume from [illegible] burial cave Tarahumara tibia or femur, grind it up and sprinkle the bone dust over part of the course which his own runners are then cautioned to avoid. The opposing team, unaware of these machinations, inadvertently steps into this area of contamination where evil spirits from the dead are reputed to reach out and seize the legs of the hapless runners.

Several of the more dramatic "end points" of physical exertion described in the literature did not seem to hold for the Tarahumara No history could be elicited which would suggest syncope as a complication of their races. Neither rupture of a previously unsuspected aneurysm nor coronary insufficiency cited as the two commonest causes of death in endurance events[1] could be substantiated in the lore or accounts of Tarahumara life. Special inquiry was made along the lines of sudden incapacitation or death attributable to an arrhythmia infarction or pulmonary edema with negative results. If there is a thermoregulatory problem—for deep body temperatures are known to rise as high as 105.8° F (41 C) in protracted exertion[4]—these Indians are unaware of it, as we were. Evidently the Tarahumara who in a real sense live by their muscles achieve a sort of special dispensation from some of these human limitations known to us.

It has been postulated that during very strenuous exertion the increase of coronary blood flow may give a greater pressure drop across any plaques in the coronary arterial tree and thus predispose to hemorrhage into the plaques. Also increased levels of circulating catecholamines as well as patchy hypoxia" of the myocardium have been suggested as causes of ventricular fibrillation and sudden death during maximal stress.[6] One might speculate that these complications are more often the result of unaccustomed exertion or at least excesses to which the performer is not sufficiently acclimated by training

A long-range limitation traditionally ascribed to athletic pursuits is cardiac enlargement. Particularly in the older medical literature there are numerous references (but little evidence) to hypertrophy of the athlete's heart" with the implication of premature death from overwork of that organ. If that were the case, surely the virtually lifelong and extreme training of the Tarahumara should give rise to conspicuous cardiac enlargement. Yet examinations of the runners at Sisoguichi disclosed no evidence of cardiac abnormality

like Nikolas. Hopefully we may derive more knowledge of this unique tribe before their culture is too diluted or swallowed up altogether in the encroaching civilization which virtually surrounds them

One physical limitation that we would expect is conspicuously absent in all accounts That is a limitation in cardiac capacity Definitely the heart is not the weakest link in the chain of Tarahumara stamina At least in this primitive setting with a people acclimated for generations to an arduous existence and conditioned since childhood to physical exploits that constitute both their livelihood and their sport cardiac symptoms as we know them are not the end point of endurance Nor it would appear are any indications of respiratory distress Indeed it may well be that more runners drop out of the contest because of superstition and fear than because of physical limitations Perhaps the Tarahumara instinctively knows what Shephard[6] has calculated in physiological terms namely that the intensity of stress imposed upon the heart by an anxiety reaction may exceed that incurred during maximum exercise and he exploits that to advantage by intimidating or frightening his opponents. Nevertheless sheer fatigue must surely take a toll though it is stoutly denied by proud contestants

One would like to have precise measurements of many physiologic responses incident to these marathons. What happens to blood volume to electrolytes to carbohydrate and lipid stores during a race of 100 miles? Does the conditioned Tarahumara have a different sort of metabolic economy which enables him to better tolerate what must be an enormous oxygen debt incurred at altitudes a mile and a half above sea level? Energy expenditure of these runners, using a rate of 11 6 Kcal per minute (equivalent to an oxygen consumption of 2 4 L. per minute which would be perhaps a conservative figure for an average pace of 6 miles per hour over such rough and hilly terrain) would calculate out at more than 11 000 Kcal for a 100 mile race A comparable estimate was arrived at by Balke and Snow[4] who pointed out that this exceeds the generally accepted limit of energy that can be expended by the most strenuous voluntary activity over a period of 24 hr So if these estimates are nearly correct we need to revise our physiological concepts of maximum-or potential-work tolerance in the human

Obviously more questions than answers are raised by these observations. Quite likely there may be arrhythmias repolarization changes injury currents or other electrocardiographic abnormalities present during and not immediately after the exertion More significant than their qualitative presence however would be the changes evoked by stress if as contended transitory disturbances of rhythm and conduction are almost universally present during normal activity in middle-aged men of our own population[7] Certainly continuous monitoring throughout a twenty four or forty eight hour marathon would be of prime interest as would a gastrocnemius biopsy thereafter One would like to know what happens to renal function as a result of this prolonged ordeal What are the effects on visceral and peripheral circulation on cardiac output cerebral blood flow oxygen transport and metabolic end products? With the recent controversy about a possible role of physical conditioning in atherogenesis and in development of coronary collateral circulation autopsy examination of hearts and arteries of these super-athletes would provide more direct evidence than any clinical data However in a situation where the limited and rudimentary medical care that is available is provided mainly by nurses in the missions such investigations must await the most urgent necessities of the living

Recently additional trips to Mexico were devoted mainly to gathering information relating to symptoms, physical complications, and sequelae of the races. Extensive interviews were carried out with several Tarahumara runners through Father Llaguno as interpreter Physicians at the Medical School of the University in Chihuahua and in the environs of that city were consulted Doubtless information gleaned in this way may reflect a bit of subjective coloring but nevertheless certain points emerge with general agreement.

No instance could be recalled of a runner ever dropping out of a race because of pain in the chest or shortness of breath Exhaustion yes and sometimes abdominal dis-

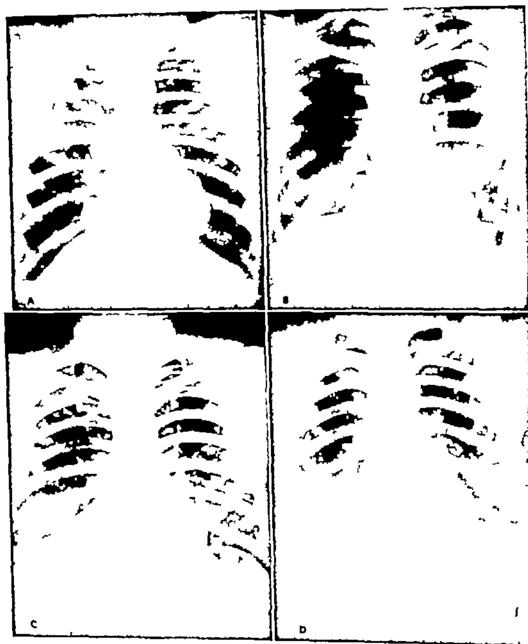


Fig. 4. A, B, C, and D. Chest x-rays on four unselected Tarahumara runners, all men, ages 22 yr (A), 40 yr (B), 45 yr (C), and 48 yr (D). All views are posteroanterior made on rather antiquated European equipment, but at the standard 2 meter tube-to-film distance.

pressure levels during and immediately after prolonged exertion

4. The phenomenal feats of physical endurance of these primitive Indian runners afford convincing evidence that most of us, brought up in our sedentary comfortable civilization of today actually develop and use only a fraction of our potential cardiac reserve.

The author owes a great debt of gratitude to the Reverend José A. Llaguno, S. J., scholar with two masters degrees and a Ph.D., who has devoted his life, as have generations of Jesuit priests before him, to the Tarahumara Indians of Mexico. He probably

either physical or electrocardiographic Chest x rays made at Norogachi on eight other Tarahumara adults most of them middle aged all showed heart shadows within normal limits as to size * Four of those films are reproduced in Fig 4 Measurements of ventricular wall thickness would of course be more conclusive but it appears from all our observations that the hearts of these Indians must respond to their increased work load in ways other than enlargement

Perhaps a little speculation would not be out of order if put forth as such First how much of the Tarahumara endurance is attributable to survival of the fittest throughout many generations of adjustment to a rigorous existence high infant mortality and natural selection? Several attempts have been made to compare them with athletes of other countries as in the 1928 Olympics but the Tarahumara are said not to perform at their utmost when brought down from their high country and bewildered by the complexities of our more regimented athletic competition Evidently few of them elect to mix with other cultures but an occasional dropout can be found like Nikolas whose upbringing has been more sheltered and sedentary and who like most of us would be left in the dust of the first lap of the race Genes alone cannot account for their stamina and diet is hardly a plausible explanation Surely the major determinant must be that of sheer physical conditioning beginning in early childhood dictated largely by necessity but carried to a degree unprecedented in modern times by competition and custom At least a partial insight into the mechanism may be found in the antithesis of conditioning just as loss of muscle strength can be shown to proceed at a rate of approximately 3 per cent per day during prolonged bed rest [4] bearing out a sort of immutable biologic law that *we lose that which we do not use* so also the converse must be true That is by intensive training started early in life and progressively increased throughout the developmental years a normal person can greatly extend the functional capacity of his muscles and doubtless his entire cardiovascular system in much the same way that the blind man develops his senses of touch and hearing or the native diver adjusts to holding his breath two minutes underwater True excellence and distinction in feats of memorization of musical performance of writing or juggling or running are seldom attained without extraordinary persistence and practice Physically the Tarahumara exemplifies that to the nth degree To him it is not a task of exercise for the sake of exercise as with so many of our urban joggers. For he has a gimmick —a wooden ball And that makes of an otherwise drab existence real fun

Conclusions

1 Most remarkable is the simple fact that the human cardiovascular system can be conditioned to withstand the extremes of endurance demonstrated in Tarahumara races of 100 miles and more Probably not since the days of the ancient Spartans has a people achieved such a high state of physical conditioning

2 Apparently the limiting somatic factor in these marathons is skeletal rather than cardiac muscle End point symptoms are predominantly cramps in the legs often accompanied by various urinary complaints. Deaths from cardiac or circulatory complications are unknown

3 Contrary to traditional belief no enlargement in these athletes hearts was evident on physical examination or x ray Also no abnormality was seen in electrocardiograms either before or immediately after a 28 mile race Why this virtually lifelong increase in work load on the heart does not cause appreciable cardiac enlargement, whereas diseases such as hypertension and aortic stenosis do is not clear nor are the mechanisms by which these runners can cope with inevitably large oxygen debts at altitudes of a mile and a half above sea level One clue to their adaptive mechanisms may lie in the observed decrease rather than increase in systolic and especially in diastolic blood

*All x-rays were made at the t o-meter distance conventional for the German equipment employed. Cardio-thoracic ratios were: 11 7 t 26.0, 11.0 to 24.2, 14.0 t 30.0, 12.0 t 28.0 cm, 39.2, 14.0 t 32.0, 12.7 to 28.5 13.3 t 29 7 12 7 t. Films of all eight subject were reviewed by staff (University of Oklahoma) radiologist and judged t show heart shadows normal in both size and contour.

The quantitative anatomy of isolated ventricular septal defect

Maurice Lev, M.D.
Robert H. Joseph, M.D.
Horacio J. A. Rimoldi, M.D., Ph.D.
Rosalia Paiva, Ph.D.
René A. Arcilla, M.D.
Chicago, Ill.

At present, a diagnosis of hypertrophy and enlargement of the cardiac chambers at autopsy is usually based on qualitative analysis. In previous reports,[1-4] we have described a quantitative method for recognizing increased chamber size and mass in a group of hearts of a single entity which we believe has more validity than qualitative estimation. Utilizing this method, we have presented the quantitative anatomy of tetralogy of Fallot,[1] the Taussig-Bing complex, and simple complete transposition of the great vessels. The present paper deals with an attempt to do likewise for isolated ventricular septal defect.

Materials and methods

We have previously presented our method in extenso. Briefly, measurements of seventeen modalities which include weight of the whole heart, sizes of chambers, thickness of walls, and sizes of the atrioventricular and semilunar orifices are made in each heart.[1] These are compared with corresponding normal values for each modality obtained from hearts of subjects of comparable age, weight, and height. A judgement is then made as to whether the values actually found in any given heart are normal, probably normal, probably abnormal, or frankly abnormal in the positive or in the negative scale.[1] In each analyzed group of cases, bar graphs are then made to indicate the proportion of cases falling into each category (normal, probably normal, probably abnormal, or abnormal).[1-4] From the latter, a decision is made as to whether a particular modality of a group of hearts being analyzed reveals a trend toward the normal or abnormal (increase or decrease). Volume indices are computed from internal measurements of chambers and are also judged as being normal or abnormal. A concept of the mass of the chamber is obtained utilizing the volume index and the thickness of the wall.

From the Congenital Heart Disease Research and Training Center, Hektoen Institute for Medical Research, the Departments of Pathology of Northwestern University Medical School, the University of Chicago School of Medicine, University of Illinois College of Medicine, the Department of Pediatrics of the University of Chicago School of Medicine, and the Loyola Psychometric Laboratory, Loyola University, Chicago, Ill.
This investigation was supported in full by Grant [illegible] and [illegible] from the National Heart Institute, National Institutes of Health, Bethesda, Md.
Received for publication April 29, 1970.
Reprint requests to: Dr. Maurice Lev, 417 S. Wood Street, Chicago, Ill. 60612.
*Career Investigator and Educator, Chicago Heart Association.

Vol. 81, No. 3, pp. 315-320, March, 1971

knows more about these people and their ways than any living Caucasian. The Padre is a warm friend and an accomplished fellow pilot without whose collaboration these studies could not have been accomplished

Special acknowledgment is due also to Dr John Steelquist of San Diego Calif who has had a long time interest in the Mission at Sisoguichi and opened many doors there by way of introductions. Also Brigadier General Franklyn S Henley USAF retired assisted in the blood pressure and pulse rate determinations Our ECGs were recorded on a portable nine-pound battery-operated electrocardiograph the "Cardioview" manufactured in England by Honeywell, Inc. This convenient little instrument (which currently is not marketed in the United States) was loaned for these studies by Dr D C Sutfin of Honeywell The chest x rays were made by nurses of the Jesuit Mission in Norogachi Chihuahua and were interpreted by Dr William A Weidner Professor of Radiology at the University of Oklahoma.

Especially we are indebted to our amazing subjects, the Tarahumara For it is they who teach us something of our own potential by providing an impressive precedent of physical conditioning—a goal that is easily neglected and lost sight of in our sedentary civilization.

REFERENCES

1 Lumholtz Carl Unknown Mexico, New York 1902 Charles Schribner s Sons.

2 Bennett, W C. and Zingg Robert M The Tarahumara, an Indian tribe of northern Mexico Chicago, 1935 University of Chicago Press.

3 Pennington Campbell W: The Tarahumara of Mexico, Salt Lake City 1963 University of Utah Press.

4 Balke B and Snow C.: Anthropological and physiological observations on Tarahumara endurance runners, Amer J Phys. Anthrop. 23:293 1965

5 Shephard R J The heart and circulation under stress of Olympic conditions, J.A.M.A 205:151 1968.

6. Kottke Frederic J: The effects of limitation of activity upon the human body J.A.M.A. 196:825 1966

7 Hinkle Lawrence E., Carver Susan T and Stevens M The frequency of asymptomatic disturbances of cardiac rhythm and conduction in middle-aged men Amer J Cardiol. 24:629 1969

The quantitative anatomy of isolated ventricular septal defect

Maurice Lev, M.D.
Robert H. Joseph, M.D.
Horacio J. A. Rimoldi, M.D., Ph.D.
Rosalia Paiva, Ph.D.
René A. Arcilla, M.D.
Chicago, Ill.

At present, a diagnosis of hypertrophy and enlargement of the cardiac chambers at autopsy is usually based on qualitative analysis. In previous reports,[1-4] we have described a quantitative method for recognizing increased chamber size and mass in a group of hearts of a single entity which we believe has more validity than qualitative estimation. Utilizing this method, we have presented the quantitative anatomy of tetralogy of Fallot, the Taussig-Bing complex, and simple complete transposition of the great vessels.[4] The present paper deals with an attempt to do likewise for isolated ventricular septal defect.

Materials and methods

We have previously presented our method in extenso. Briefly, measurements of seventeen modalities which include weight of the whole heart, sizes of chambers, thickness of walls, and sizes of the atrioventricular and semilunar orifices are made in each heart.[1] These are compared with corresponding normal values for each modality obtained from hearts of subjects of comparable age, weight, and height. A judgment is then made as to whether the values actually found in any given heart are normal, probably normal, probably abnormal, or frankly abnormal in the positive or in the negative scale. In each analyzed group of cases, bar graphs are then made to indicate the proportion of cases falling into each category (normal, probably normal, probably abnormal, or abnormal).[1-4] From the latter, a decision is made as to whether a particular modality of a group of hearts being analyzed reveals a trend toward the normal or abnormal (increase or decrease). Volume indices are computed from internal measurements of chambers and are also judged as being normal or abnormal. A concept of the mass of the chamber is obtained utilizing the volume index and the thickness of the wall.

From the Congenital Heart Disease Research and Training Center, Hektoen Institute for Medical Research, the Departments of Pathology of Northwestern University Medical School, the University of Illinois College of Medicine, the Department of Pediatrics of the University of Chicago School of Medicine, and the Loyola Psychometric Laboratory, Loyola University, Chicago, Ill.

This investigation was supported in full by Grants HE-07605-08 and HE-5139-08 from the National Heart Institute, National Institutes of Health, Bethesda, Md.
Received for publication April 29, 1970.

Reprint requests to: Dr. Maurice Lev, 37 E. Wood Street, Chicago, Ill. 606 1.
*Career Investigator and Educator, Chicago Heart Association.

Am. Heart J. 81: No. 3, pp. 315-320, March, 1971

Fifty three cases of ventricular septal defect (VSD) were examined These were limited to those of patients above 3 months of age since physiologic considerations are quite different in the transition period (birth to 3 months of age) The anatomic findings were analyzed according to the following (1) position of the defect (2) size of defect relative to that of the aortic orifice and (3) presence or absence of over riding Of the 53 patients 24 had cardiac catheterization studies The findings in the latter cases were also analyzed according to (1) size of shunt (2) pulmonary arterial pressure and (3) pulmonary resistance Left to-right shunting was empirically classified as small = Q_p/Q ratio of less than 2 1 moderate = Q_p/Q ratio of 2 to 2 7 1 and large = Q_p/Q ratio of more than 2 7 1 Pulmonary arterial mean pressure was likewise classified as (1) normal = less than 25 per cent of systemic (2) mildly increased = 25 per cent to 50 per cent of systemic (3) moderately increased = 50 to 75 per cent of systemic and (4) markedly increased = above 75 per cent of systemic Resistance was classified as normal = less than 25 per cent of systemic mildly elevated = 25 per cent to 33 per cent of systemic moderately elevated = 33 per cent to 75 per cent of systemic and markedly elevated = above 75 per cent of systemic.

Findings

General Heart weight was increased in all groups Right ventricular enlargement was consistently associated with increased wall thickness and volume Left ventricular enlargement was also generally present consisting predominantly of an increase of volume but minimal or no increase of wall thickness. Enlargements of the pulmonary and mitral valve orifices were generally present but no consistent changes in the tricuspid and aortic valve orifices were observed

Position of VSD (sinus versus conus defects) In order to evaluate the effect of the position of the defect, the materials were grouped into those where the defect opened definitely into the sinus and those where it opened into the conus (thus excluding the cases where the defect was

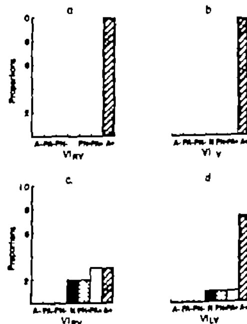


Fig 1 *a b c* and *d* Bar graphs depicting proportion of cases in which the volume index of the right and left ventricles fell into various categories (*A*– *PA*– *PN*– N *PN*+ *PA*+ *A*+) in ventricular septal defects opening into the sinus and conus. In a and *b* sinus defects are shown *c* and *d* indicate conus defect VI_{RV} = volume index of right ventricle VI_{LV} = volume index of left ventricle A– = definitely decreased *PA*– = probably decreased *PN*– = probably normal in the negative scale N = definitely normal *PN*+ = probably normal in the positive scale *PA*+ = probably increased A+ = definitely increased

situated at the sinus-conus junction) Generally speaking the volume of the right ventricle was greater in the sinus group (Fig 1) than in the conus group although the increase in wall thickness was approximately comparable in both groups. Left ventricular enlargement was also somewhat greater in the sinus than in the conus defects. The pulmonary and mitral valve orifices were enlarged in both groups with comparatively greater enlargement of the pulmonary orifice in the sinus defects. The size of the tricuspid and aortic valve orifices varied widely and failed to reveal any consistent change pattern in both groups. There appeared to be some tendency for the tricuspid valve orifice to be slightly larger in sinus defects

Relative size of VSD $\left(\frac{\text{maximal diameter of defect}}{\text{aortic valve circumference}}\right)$

The relative size of the defect was estimated by taking the ratio of its maximal diameter to that of the circumference of the



Fig. 2 a, b, c, and d. Bar graphs showing proportion of cases in which the thickness of the right ventricle fell into various categories, as in Fig. 1, in ventricular septal defect of certain sizes. a and b, where $\frac{\text{size of VSD}}{\text{aortic orifice}}$ = 0.00 to 0.20; c and d, where $\frac{\text{size of VSD}}{\text{aortic orifice}}$ = 0.20 to 0.30. RV P = thickness of right ventricle at the pulmonic area. RV T = thickness of right ventricle at the tricuspid area.

aortic valve ring. When correlated with the observed hemodynamic data, the cases with normal or mildly elevated pulmonary arterial pressures had defect: aortic orifice ratios ranging from 0.09 to 0.16 (mean 0.11); those with moderate pulmonary hypertension had ratios ranging from 0.11 to 0.37 (mean 0.25); and those with severe pulmonary hypertension and elevated pulmonary resistance had ratios ranging from 0.20 to 0.43 (mean 0.32).

In the cases where the defect: aortic ratio was 0.20 or less, some right ventricular enlargement consisting of increased wall thickness and volume was noted (Figs. 2 and 3). The increase in volume was comparatively greater in the left ventricle than

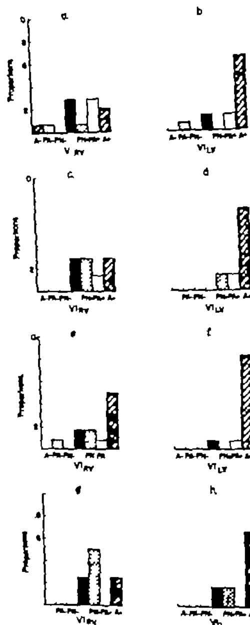


Fig. 3 a, b, c, d, e, f, g, and h. Bar graphs depicting the proportion of cases in which the volume index of the right and left ventricles fell into various categories, as in Fig. 1, in ventricular septal defects of various sizes. a and b, where $\frac{\text{size of VSD}}{\text{aortic orifice}}$ = 0.00 to 0.20; c and d, where $\frac{\text{size of VSD}}{\text{aortic orifice}}$ = 0.20 to 0.30; e and f, where $\frac{\text{size of VSD}}{\text{aortic orifice}}$ = 0.30 to 0.50; g and h, where $\frac{\text{size of VSD}}{\text{aortic orifice}}$ = more than 0.5. VI_{RV} = volume index of right ventricle. VI = vol me index of left ventricle.

in the right ventricle The pulmonary and mitral valve orifices were enlarged but the tricuspid orifice appeared normal There was a tendency for the aortic valve orifice to be somewhat enlarged

In the cases where the defect aortic ratio was 0 21 to 0 30 right and left ventricular enlargement and thickness was comparatively greater than in the preceding group (Figs 2 and 3) The enlargement of the pulmonary and mitral valve orifices was also comparatively greater in this group than in the preceding one The size of the tricuspid and aortic orifices appeared normal

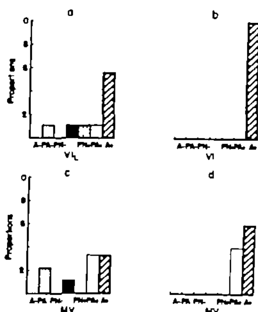


Fig 4 a b c and d Bar graphs depicting the proportion of cases in which the volume index of the left ventricle (VI_{LV}) and the size of the mitral orifice (MV) fell into various categories as in Fig 1 dependent upon size of shunt a and c size of shunt—small b size of shunt—moderate and d size of shunt large.

In the cases with a defect aortic ratio of 0 31 to 0 50 the increase in the volume index of the left ventricle was about similar to that in the preceding group with its wall thickness still remaining normal Right ventricular enlargement however was greater also with greater thickness of its wall The enlargement of the pulmonary and mitral valve orifices was about similar to that of the preceding group The tricuspid and aortic valve orifices appeared slightly enlarged

In those with a defect aortic ratio of more than 0 50 the left ventricular enlargement was not as much as in the second and third groups Right ventricular volume was also smaller than in the preceding group although wall thickness was the same The pulmonary orifice appeared equally enlarged but the mitral orifice was about normal The tricuspid valve orifice was slightly enlarged but the aortic orifice had a tendency to be somewhat smaller than normal

Overriding of aorta There was no remarkable difference between cases with and without overriding except that the aorta was somewhat larger in cases with overriding

Size of shunt pulmonary arterial pressure and pulmonary vascular resistance The relative size of the systemic to pulmonary shunt showed a positive correlation with the enlargement of both ventricles (Fig 4) while pulmonary arterial pressure and resistance correlated well with thickness of the right ventricle (Figs. 5 and 6)

Left ventricular enlargement consisting



Fig 5 a b and c. Bar graphs depicting the proportion of cases in which the thickness of the right ventricle fell into various categories, as in Fig 1 dependent upon the pulmonary pressure, a with normal or mildly increased pulmonary pressure b with moderately increased pulmonary pressure and c with markedly increased pulmonary pressure. $RV\ P$ = thickness of right ventricle at the pulmonic area.

chiefly of increased volume and normal or slight increase of wall thickness, was greater in the patients with moderate or large shunts as compared to those with small shunts. The mitral orifice was normal or slightly enlarged in the latter cases but was definitely enlarged in the cases of moderate or large shunts (Fig 4) The aortic orifice was normal in those with small shunts but was slightly enlarged in those with moderate or large shunts.

In the cases with normal or mildly elevated pulmonary arterial pressures right ventricular enlargement was present with some increase of wall thickness. The volume of the right ventricle increased with moderately increased pressure but was smaller in the cases with markedly increased pressure, although wall thickness was greater The pulmonary orifice also was grossly enlarged with increased pressure the tricuspid orifice remained normal. The same findings were true for increased resistance.



Fig. 6 *a*, *b*, *c*, and *d*. Bar graphs depicting the proportion of cases in which the thickness of the right ventricle fell into various categories, as in Fig. 1 dependent upon the degree of pulmonary resistance. *a* and *b*, with pulmonary resistance normal, or mildly increased, and *c* and *d* with pulmonary resistance moderately increased. *RV P* = thickness of right ventricle at the pulmonic area. *RV T* = thickness of right ventricle at the tricuspid area.

Thus in the cases with normal or mildly elevated pulmonary arterial pressures and normal pulmonary vascular resistance, mild right and left ventricular enlargement were present with some thickening of the right but not of the left ventricular wall. The pulmonary tricuspid and aortic orifices showed variable changes in size the mitral orifice appeared slightly enlarged the cases with moderate or marked pulmonary hypertension but normal or slightly increased pulmonary vascular resistance revealed greater right ventricular enlargement and wall thickening. The pulmonary orifice appeared larger and the mitral orifice somewhat greater as compared to that observed in the preceding group The left ventricle was enlarged but its wall did not reveal significantly increased thickening The tricuspid and aortic orifices appeared normal. Those with marked pulmonary hypertension and moderately elevated pulmonary vascular resistance revealed similar findings as the preceding group. One case with severe pulmonary vascular obstruction showed marked thickening of the right ventricular wall and small cavity normal left ventricular size and small valve orifices except the aortic which appeared normal

Discussion

The quantitative anatomy of ventricular septal defect in general corresponds to what one would expect from the hemodynamic findings, although certain questions remain unanswered.

It is clear that patients with normal or slightly increased pulmonary pressure and normal pulmonary resistance develop volume and, in some cases, pressure hypertrophy of the right ventricle and volume hypertrophy of the left ventricle. This is accompanied by enlargement of the pulmonic and mitral valve orifices. The dilatation of the pulmonary orifice appears to be due not only to the increased right ventricular stroke flow across it but also to the pulmonary hypertension that of the mitral orifice must be due to the increased left ventricular volume load It is also clear that when the pulmonary pressure is increased but the resistance is still normal or mildly elevated similar changes occur with the increase in pressure hypertrophy

in the right ventricle The pulmonary and mitral valve orifices were enlarged but the tricuspid orifice appeared normal There was a tendency for the aortic valve orifice to be somewhat enlarged

In the cases where the defect aortic ratio *was 0 21 to 0 30* right and left ventricular enlargement and thickness was comparatively *greater than in the preceding group* (Figs 2 and 3) The enlargement of the pulmonary and mitral valve orifices was also comparatively greater in this group than in the preceding one The size of the tricuspid and aortic orifices appeared normal

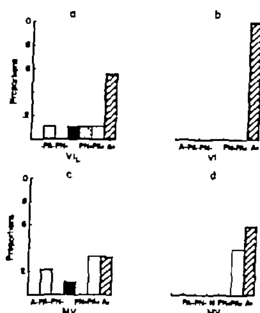


Fig *4 a b c* and *d* Bar graphs depicting the proportion of cases in which the volume index of the left ventricle (*VI LV*) and the size of the mitral orifice (*MV*) fell into various categories, as in Fig *1* dependent upon size of shunt *a* and *c* size of shunt–small *b* size of shunt–moderate and *d* size of shunt–large.

In the cases with a defect aortic ratio of 0 31 to 0 50 *the increase in the volume* index of the left ventricle was about similar to that in the preceding group with its wall thickness still remaining normal Right ventricular enlargement however was greater also with greater thickness of its wall The enlargement of the pulmonary and mitral valve orifices was about similar to that of the preceding group The *tricuspid and aortic valve orifices appeared* slightly enlarged

In those with a defect aortic ratio of more than 0 50 the left ventricular enlargement was not as much as in the second and third groups Right ventricular volume was also smaller than in the preceding group although wall thickness was the same. The pulmonary orifice appeared equally enlarged but *the mitral orifice* was about normal The tricuspid valve orifice was slightly enlarged but the aortic orifice had a tendency to be somewhat smaller than normal

Overriding of aorta There was no remarkable difference between cases with and without *overriding except that the aorta* was somewhat larger in cases with overriding

Size of shunt pulmonary arterial pressure and pulmonary vascular resistance The relative size of the systemic to pulmonary shunt showed a positive correlation with the enlargement of both ventricles *(Fig 4)* while pulmonary arterial pressure and resistance correlated well with thickness of the right ventricle (Figs. 5 and 6)

Left ventricular enlargement, consisting

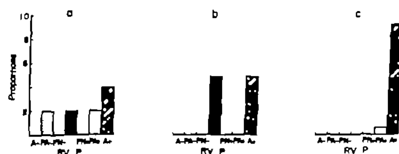


Fig *5 a, b* and *c* Bar graphs depicting the proportion of cases in which the thickness of the right ventricle fell into various categories as in Fig *1* dependent upon the pulmonary pressure, *a*, with normal or mildly increased pulmonary pressure *b* with moderately increased pulmonary pressure and *c*, with markedly increased pulmonary pressure. *RV P* = thickness of right ventricle at the pulmonic area.

Tetralogy of Fallot and heart failure

E. Chesler, M.D. (Rand), F.R.C.P. (Edin.)
H. S. Joffe, M.B., Ch.B., M.Med. (Paed.)
W. Beck, M.Sc., M.Med., M.R.C.P., F.A.C.C.
V. Schrire, M.Sc., Ph.D., M.D., F.R.C.P.E., F.R.C.P., F.A.C.C.
Cape Town, South Africa

Among patients with cyanotic congenital heart disease the presence of congestive cardiac failure is said to preclude the diagnosis of tetralogy of Fallot. Occasionally heart failure may occur in infants with tetralogy of Fallot when there is superadded bacterial endocarditis, anemia,[1] or systemic hypertension. Uncommon anatomical variants such as aortic insufficiency, absence of the pulmonary valve or one pulmonary artery, or functional obstruction of the ventricular septal defect by the tricuspid valve[2] may also predispose to this complication.

We have encountered 6 patients with tetralogy of Fallot in whom heart failure could not be ascribed to the factors mentioned above. This report describes the clinical, radiological, and hemodynamic features of these patients.

Materials and methods

The 6 patients presented in this report were encountered among 365 cases of tetralogy of Fallot investigated in our clinic. Of the patients, 191 were Caucasian, 133 Cape colored (mulatto), and 41 Bantu. History, physical examination, roentgenograms, electrocardiograms, phonocardiograms, cardiac catheterization, and angiograms were available in all 6 cases. Necropsy findings were available in 2 cases and operative findings in 3 cases.

Results

Age, sex, and race. The patients' ages ranged from 16 months to 14 years (Table I). Five patients were Bantu and 1 Cape colored. Three were boys and 3 were girls.

History and physical findings. Dyspnea was a symptom in all patients. Two patients (Patients 2 and 6) had received digitalis and diuretics prior to admission to our unit and in these heart failure was not evident clinically, although the jugular venous pressure was elevated in Patient 6. In the remaining 4 patients, there was clinical evidence of cardiomegaly, raised venous pressure, and hepatomegaly. All the patients were cyanosed and their fingers and toes were clubbed. Cyanotic spells culminating in marked acidosis was a feature in three of these infants. These spells were severe enough to require resuscitation with sodium bicarbonate, propranolol, and morphine.

Auscultation of the heart and phono-

From the Cardio-Pulmonary Unit, Groote Schuur Hospital, Departments of Medicine and Paediatrics, University of Cape Town and the Cardiovascular-Pulmonary Research Group, Cape Town, South Africa.

Supported by the Department of Medicine by the South African Medical Research Council.
Received for publication May 8, 1970.

Reprint requests to: Dr. E. Chesler, University of Cape Town, Cardiac Clinic, Groote Schuur Hospital, Observatory, Cape Town, South Africa.

Vol. 81, No. 3, pp. 321-326, March 1971

of the right ventricle being strikingly more. With increasing pulmonary vascular obstruction the right ventricle becomes thicker at the expense of its volume and the volume changes in the left ventricle are no longer as apparent There is no adequate explanation for the enlargement of the aortic orifice observed in some cases. Whether unsuspected aortic insufficiency of a mild degree is a contributory factor is not known

It is difficult to separate the effect of the shunt and the pulmonary pressure upon the cardiac anatomy but it would appear that the thrust of a left to-right shunt is volume change in both ventricles while the effect of increasing pulmonary pressure is thickness of the wall of the right ventricle as one would expect. The main effect of increased pulmonary resistance is greater thickness of the wall of the right ventricle and conversely decreased volume changes of the left ventricle after a certain point

It is also evident that the larger the defect the greater are the changes related to shunt pressure and resistance until a certain degree of pulmonary vascular obstruction is reached when the volume changes on the left side gradually diminish

Of interest is the finding that defects which enter the sinus area tend to produce more volume changes on the right side than those which enter the conus. It may also be noted that the tricuspid orifice may be somewhat more enlarged in sinus defects. These findings tend to suggest that volume overloading of the right ventricle may be comparatively greater in sinus defects. Our data does not substantiate at least from indirect evidence a greater tendency for pulmonary hypertension in conus defects. This statement is of course predicated on an assumption that the size of the defects in the two groups of patients were comparable This assumption may be subject to question since the estimation of the size of the defects in our material was not made in the fresh state and consequently were subject to subtle postmortem and postfixation artifactual changes. This is the same reason why in evaluating the effect of defect size only the maximal diameter of the VSD was estimated and related to the aortic valve circumference and why the cases were categorized into four widely separated groups.

REFERENCES

1 Rowlatt, U F Rimoldi H J A and Lev M The quantitative anatomy of the normal child's heart Pediat Clin. N Amer 10:499 1963

2 Rimoldi, H J A. and Lev M A note on the concept of normality and abnormality in quantitation of pathologic findings in congenital heart disease Pediat Clin N Amer 10:589 1963

3 Lev M Rimoldi H J A. and Rowlatt U F The quantitative anatomy of cyanotic tetralogy of Fallot Circulation 30:531 1964.

4 Lev M Rimoldi H J A Eckner F A O Melhuish B P Meng C C L and Paul M H: The Taussig Bing heart qualitative and quantitative anatomy A.M A. Arch Path. 81:24 1966.

5 Lev M Rimoldi H. J A Paiva R. and Arcilla R. A. The quantitative anatomy of simple complete transposition Amer J Cardiol. 23 409 1969

Tetralogy of Fallot and heart failure

E. Chesler, M.D. (Rand.), F.R.C.P. (Edin.)
H. S. Joffe, M.B., Ch.B., M.Med. (Paed.)
W. Beck, M.Sc., M.Med., M.R.C.P., F.A.C.C.
V. Schrire, M.Sc., Ph.D., M.D., F.R.C.P.E., F.R.C.P., F.A.C.C.
Cape Town, South Africa

Among patients with cyanotic congenital heart disease the presence of congestive cardiac failure is said to preclude the diagnosis of tetralogy of Fallot. Occasionally heart failure may occur in infants with tetralogy of Fallot when there is superadded bacterial endocarditis,[1] anemia, or systemic hypertension. Uncommon anatomical variants such as aortic insufficiency, absence of the pulmonary valve or one pulmonary artery,[3] or functional obstruction of the ventricular septal defect by the tricuspid valve[4] may also predispose to this complication.

We have encountered 6 patients with tetralogy of Fallot in whom heart failure could not be ascribed to the factors mentioned above. This report describes the clinical, radiological, and hemodynamic features of these patients.

Materials and methods

The 6 patients presented in this report were encountered among 365 cases of tetralogy of Fallot investigated in our clinic. Of the patients, 191 were Caucasian, 133 Cape colored (*mulatto*), and 41 Bantu. History, physical examination, roentgenograms, electrocardiograms, phonocardiograms, cardiac catheterization, and angiograms were available in all 6 cases. Necropsy findings were available in 2 cases and operative findings in 3 cases.

Results

Age, sex, and race. The patients' ages ranged from 16 months to 14 years (Table I). Five patients were Bantu and 1 Cape colored. Three were boys and 3 were girls.

History and physical findings. Dyspnea was a symptom in all patients. Two patients (Patients 2 and 6) had received digitalis and diuretics prior to admission to our unit and in these, heart failure was not evident clinically, although the jugular venous pressure was elevated in Patient 6. In the remaining 4 patients there was clinical evidence of cardiomegaly, raised venous pressure, and hepatomegaly. All the patients were cyanosed and their fingers and toes were clubbed. Cyanotic spells culminating in marked acidosis was a feature in three of these infants. These spells were severe enough to require resuscitation with sodium bicarbonate, propranolol, and morphine.

Auscultation of the heart and phono-

From the Cardio-Pulmonary Unit, Groote Schuur Hospital, Departments of Medicine and Paediatrics, University of Cape Town and the Cardiovascular-Pulmonary Research Group, Cape Town, South Africa.
Supported in the Department of Medicine by the South African Medical Research Council.
Received for publication May 8, 19[illegible].
Reprint requests to: Dr. E. Chesler, University of Cape Town, Cardiac Clinic, Groote Schuur Hospital, Observatory, Cape Town, South Africa.

Table I Hemodynamic data

Patient	Age	Pressures (mm Hg)						Flows		(%) R L shunt	Systemic saturation (%)	Hb. Gm. %
		RA	RV	PA	Wedge	Aorta	Brachial artery	Systemic	Pulmonary			
1	10 mo	22	127/13-1	96/71*	11	127/75	—	3.8	1.9	65	67	12.8
2	22 mo.	13	97/8-11	—	—	—	—	—	—	—	51	18.1
3	30 mo	14	65/15-23	32/25	18	—	93/63	4.8	2.9	22	74	11.3
4	33 mo.	4.5	123/5	11/8	4	123/50	—	4.	1.04	50	67.5	13.4
5	7 yr	15	100/8-10	16	—	100/75	120/80	14	1.5	43	57.5	19
6	14 yr	11	131/14	—	—	—	141/90	4.75	1.7	75	63	17

RA = Right atrium; RV = Right ventricle; PA = pulmonary artery; and Hb. = hemoglobin.
*Spontaneous pulsus alternans noted in right ventricular and aortic pressures

cardiograms revealed short ejection systolic murmurs ending well before the aortic component of the second heart sound in 4 cases. In 2 cases there were continuous murmurs which arose from enlarged bronchial arteries in Patient 5 and from a previous Blalock Taussig operation in Patient 6 The second sound in all cases consisted of the aortic component only pulmonary closure was universally absent Diastolic gallop rhythm was audible in 2 patients (Patients 3 and 5) There was no evidence of bacterial endocarditis in any of the patients.

Laboratory investigations The hemoglobin levels are given in Table I The lowest hemoglobin level was 11 3 Gm per cent (Patient 3) All the erythrocyte sedimentation rates and white cell counts were within normal limits.

The electrocardiogram All the patients were in sinus rhythm The mean frontal plane QRS axis was normal in one patient (+80 degrees) In the remaining patients the axes lay between +130 and +190 degrees All the tracings showed evidence of right atrial enlargement and right ventricular hypertrophy Tall R waves were present in Lead V_1 and characteristically there was an early transition zone to an R_s pattern in precordial Leads V_2 or V_3 In none of the patients were there abnormalities of intraventricular or atrioventricular conduction The tracings did not differ significantly from those encountered in the remaining 359 cases of tetralogy investigated by us.

Radiology In none of the patients were the radiological findings typical of those usually observed in tetralogy of Fallot Pulmonary oligemia was present in all cases except Patient 3 (Fig 1 C) in whom there was evidence of pulmonary congestion The outstanding abnormality was the enlargement of the cardiac silhouette (Fig 1) In Patient 1 the cardiac outline almost filled the chest and resembled a pericardial effusion In Patients 2 to 6 the cardiothoracic ratios were 62 per cent 75 per cent 66 per cent 69 per cent and 65 per cent respectively

Cardiac catheterization and angiography Cardiac catheterization was performed under sedation and the hemodynamic data are given in Table I The pulmonary artery was not entered in two cases. This was because of a severe cyanotic spell shortly after the commencement of catheterization in Patient 2 and because of technical difficulty in Patient 6 In the remaining 4 cases withdrawal tracings from the pulmonary artery to the right ventricle demonstrated infundibular stenosis in 3 cases and valve stenosis in one.

In none of the cases did the peak systolic pressure in the right ventricle exceed that of the aorta or the brachial artery (Withdrawal tracings were found from aorta to right ventricle in 3 cases and simultaneously recorded aortic and right ventricular pressures in one case)

End-diastolic pressures in the right ventricle and the right atrial pressures were elevated in all patients except Patient

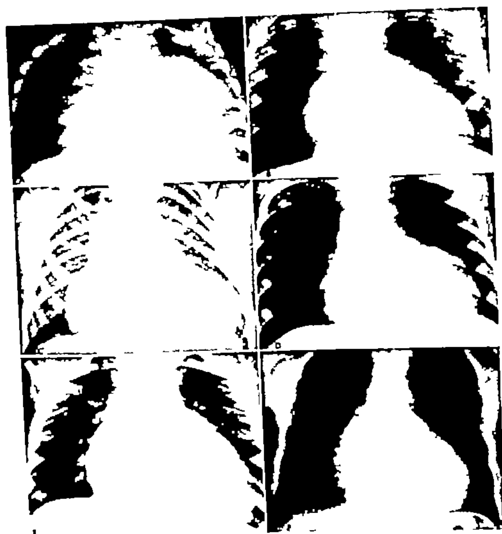


Fig. 1 Roentgenograms of chest Anteroposterior view Patients 1 to 6 (*A* t *F* respectively)

4 This infant had received digitalis and diuretics, which probably accounts for these findings there was, however evidence of impaired myocardial contractility in that pulsus alternans was present in the right ventricular and aortic pressures and, in addition right ventricular angiography showed a large poorly contracting chamber Spontaneous pulsus alternan was also observed in the right ventricular and aortic pressures in Patient 5

Systemic desaturation resulting from right to-left shunting was present in every case (Table I)

Angiograms performed from the right ventricle showed features usually observed in the tetralogy of Fallot, namely in fundibular stenosis in every case, and additional valve stenosis in 3 cases. The aorta was dextroposed but never transposed and the pulmonary valve was always higher than the aortic valve Patient 6 behaved functionally like pulmonary atresia acquired after a previous Blalock Taussig operation The right ventricular outflow tract was completely occluded during systole by infundibular contraction the pulmonary artery filling in diastole only during atrial contraction.

The outstanding angiographic abnormality was the marked dilatation and poor contractility of the right ventricle seen in both the anteroposterior and lateral views (Figs. 2 and 3) In Patient 3 (Fig 3) right

Table I Hemodynamic data

Patient	Age	Pressures (mm Hg)						Flows		(%) R-L shunt	Systemic saturation (%)	Hb. Gm. %
		RA	RV	PA	Wedge	Aorta	Brachial artery	Systemic	Pulmonary			
1	18 mo	22	177/13- 1	[illegible]/21	11	177/75	—	3 8	1 9	65	67	12 8
2	22 mo.	13	93/ 8-11	—	—	—	—	—	—	—	21	19 3
3	30 mo	14	88/15-[illegible]	32/[illegible]	18	—	93/63	4 8	9	22	74	11 3
4	33 mo.	4 5	[illegible]/ 5	11/ 8	4	125/80	—	4	1 05	60	67 5	15 5
5	7 yr	15	100/ 8-10	16	—	100/75	120/80	14	1 6	43	87 5	19
6	14 yr	11	131/14	—	—	—	141/90	4 75	1 7	75	63	21 7

RA = Right atrium RV = right ventricle; PA = pulmonary artery; and Hb = hemoglobin.
*Spontaneous pulsus alternans noted in right ventricular and aortic pressures.

cardiograms revealed short ejection systolic murmurs ending well before the aortic component of the second heart sound in 4 cases In 2 cases there were continuous murmurs which arose from enlarged bronchial arteries in Patient 5 and from a previous Blalock Taussig operation in Patient 6 The second sound in all cases consisted of the aortic component only pulmonary closure was universally absent Diastolic gallop rhythm was audible in 2 patients (Patients 3 and 5) There was no evidence of bacterial endocarditis in any of the patients

Laboratory investigations The hemoglobin levels are given in Table I The lowest hemoglobin level was 11 3 Gm per cent (Patient 3) All the erythrocyte sedimentation rates and white cell counts were within normal limits.

The electrocardiogram All the patients were in sinus rhythm The mean frontal plane QRS axis was normal in one patient (+80 degrees) In the remaining patients the axes lay between +130 and +190 degrees. All the tracings showed evidence of right atrial enlargement and right ventricular hypertrophy Tall R waves were present in Lead V_1 and characteristically there was an early transition zone to an R pattern in precordial Leads V_2 or V_3 In none of the patients were there abnormalities of intraventricular or atrioventricular conduction The tracings did not differ significantly from those encountered in the remaining 359 cases of tetralogy investigated by us.

Radiology In none of the patients were the radiological findings typical of those usually observed in tetralogy of Fallot Pulmonary oligemia was present in all cases except Patient 3 (Fig 1 C) in whom there was evidence of pulmonary congestion The outstanding abnormality was the enlargement of the cardiac silhouette (Fig 1) In Patient 1 the cardiac outline almost filled the chest and resembled a pericardial effusion In Patients 2 to 6 the cardiothoracic ratios were 62 per cent 75 per cent 66 per cent 69 per cent and 65 per cent respectively

Cardiac catheterization and angiography Cardiac catheterization was performed under sedation and the hemodynamic data are given in Table I The pulmonary artery was not entered in two cases. This was because of a severe cyanotic spell shortly after the commencement of catheterization in Patient 2 and because of technical difficulty in Patient 6 In the remaining 4 cases withdrawal tracings from the pulmonary artery to the right ventricle demonstrated infundibular stenosis in 3 cases and valve stenosis in one

In none of the cases did the peak systolic pressure in the right ventricle exceed that of the aorta or the brachial artery (Withdrawal tracings were found from aorta to right ventricle in 3 cases and simultaneously recorded aortic and right ventricular pressures in one case)

End-diastolic pressures in the right ventricle and the right atrial pressures were elevated in all patients except Patient

stenosis in both cases and severe valve stenosis in Patient 3 a large ventricular septal defect and over riding of a dextroposed aorta In both cases the walls of the ventricles were hypertrophied and their cavities markedly dilated Antemortem thrombi were not found. Mild subendocardial and papillary muscle fibrosis was present but there was no evidence of viral myocarditis or interstitial fibrosis.

Discussion

In tetralogy of Fallot the right ventricle never has to eject against more than the systemic resistance irrespective of the severity of the pulmonary stenosis. For this reason heart failure in the absence of complications or associated malformations is universally absent. One of the most constant features is the radiological evidence of a normal heart size. Indeed significant cardiomegaly in a patient with cyanotic heart disease is usually sufficient evidence to preclude the diagnosis of tetralogy.[1] Prior to cardiac catheterization, evidence of heart failure and cardiomegaly in our cases led to considerable diagnostic difficulty and conditions, such as transposition with pulmonary stenosis and pulmonary stenosis with intact ventricular septum were considered

In our patients the elevated right atrial pressure and high-end-diastolic pressure in the right ventricle could not be ascribed to a small ventricular septal defect or a ventricular septal defect closed in systole by the septal leaflet of the tricuspid valve since the peak systolic pressure in the right ventricle did not exceed that of the aorta or the brachial artery the findings are therefore a reflection of myocardial failure. Additional evidence of impaired myocardial contractility was present in the form of pulsus alternans and poor contraction of the ventricles observed angiographically In none of the cases was there severe anemia[7] or evidence of conditions such as bacterial endocarditis, aortic insufficiency absence of a pulmonary artery or pulmonary valve, which have been reported to lead to cardiomegaly and heart failure

Heart failure in tetralogy has also been ascribed to systemic hypertension by Holladay and Witham who reported 12 cases with hypertension in patients whose ages varied from 2 to 18 years of these 6 died in heart failure. The blood pressure levels obtained were in excess of the average blood pressures expected in the various age-groups. In 5 patients the diastolic pressures varied from 115 to 140 mm Hg in the remaining patients, however the diastolic pressures varied between 80 to 100 mm Hg The blood pressures recorded in our patients are comparable allowing for the fact that in 2 instances readings were recorded from the aorta where peripheral amplification is not present. We are inclined to believe however that systemic hypertension with diastolic figures of less than 110 mm Hg is a manifestation and not a cause of heart failure *and results* from increased systemic vascular resistance It is interesting to note that the patients described by the above authors were also Negroes. Five of our patients were Bantu and one colored In our material this racial predilection is especially significant since Bantu patients constitute only 11 *per cent* of all cases of tetralogy of Fallot investigated in our Clinic

Congestive cardiomyopathy is not uncommon in the American Negro and may affect the younger age groups.[8] In the South African Bantu it is a very common form of heart disease [11] and is said to be more rapidly progressive in children [12] The disease also occurs frequently in the Cape colored At necropsy these hearts showed dilatation and hypertrophy with slight subendocardial fibrosis antemortem *thrombus* may be present on the ventricular myocardium. The findings in our 2 cases where necropsies were available are compatible with this disease. We believe therefore that the explanation for the heart failure in our cases of tetralogy is not related to the malformation itself or to any of the complications mentioned previously but rather to the superimposition of cardiomyopathy in an ethnic group prone to this disease It is possible that some of the cases occurring in the American Negro and ascribed to systemic hypertension may have a similar basis.[8]

Summary

The clinical, radiological and hemodynamic features of 6 cases of tetralogy of Fallot complicated by heart failure is de

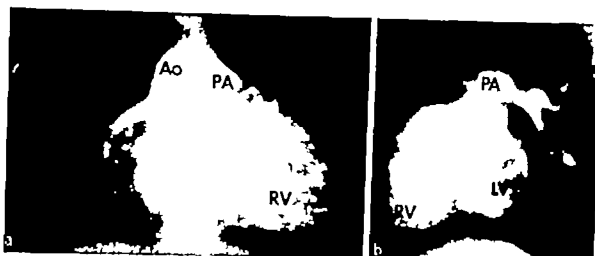


Fig 2 *a* and *b* Right ventricular angiocardiogram Patient 2 *a* and *b* frontal and lateral views respectively showing unusual dilatation of right ventricle Infundibular and pulmonary valve stenosis
RV = right ventricle *LV* = left ventricle *Ao* = aorta and *PA* = pulmonary artery

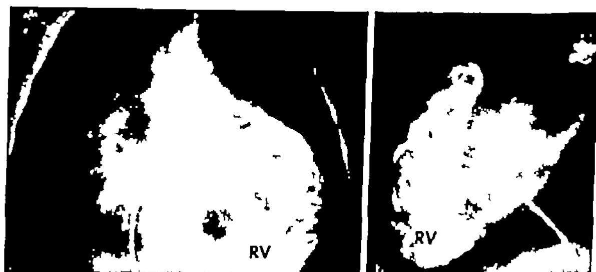


Fig 3 *a* and *b* Right ventricular angiocardiogram Patient 3 *a* and *b* frontal and lateral views, respectively showing large dilated right ventricle (*RV*) which hardly altered in size during systole and diastole.

ventricular contraction was particularly poor resulting in prolonged retention of contrast material spill-over of dye into the left ventricle through the ventricular septal defect showed poor contraction of this chamber as well The latter finding correlated with hemodynamic evidence of left ventricular disease in this patient where the pulmonary artery pressure was 32/25 mm Hg and the wedge pressure 18 mm Hg

Clinical course Patients 3 and 4 died within 24 hours of cardiac catheterization Patient 1 died in heart failure two months after investigation The remaining 3 patients were submitted to open heart surgery and pulmonary valvotomy resection of infundibular stenosis and closure of the ventricular septal defect were performed Patient 2 died suddenly 72 hours after surgery an unusual degree of dilatation of the right ventricle was noted by the surgeon in this case Patient 5 had a stormy postoperative course and remains in heart failure Patient 6 made a satisfactory postoperative recovery but is left with radiological evidence of cardiomegaly

Pathology Autopsies were performed on Patients 3 and 4 In Patient 3 the heart weighed 182 grams and in Patient 4 166 grams Both patients showed malformations characteristic of tetralogy of Fallot namely right ventricular outflow tract obstruction in the form of infundibular

Backward transmission of the left atrial V wave and premature pulmonary valve closure

Donald A. Spring, M.D.
George G. Rowe, M.D.
Madison, Wis.

In the normal subject, pulmonary valve closure does not occur until right ventricular pressure decreases at the end of systolic ejection. In some cases analysis of the relationship between right ventricular and pulmonary artery pressures shows an abnormality which may alter the time of pulmonary valve closure. Early pulmonary valve closure was suggested upon the study of the hemodynamic records of two subjects from a group of five who were shown by cardiac catheterization to have severe mitral insufficiency. This unusual phenomenon is the basis of the present report (see Fig. 1, left panel).

Materials and methods

In addition to clinical examination, phonocardiographic records were made in three subjects utilizing a Sanborn 650 Visso A Phonocardiograph. Right and left ventricular apex cardiograms were recorded by means of a Model 373 Hewlett Packard pulse wave transducer attachment with a manually positioned funnel shaped pickup. Standard right heart as well as retrograde left and transseptal left heart catheterizations were performed in all patients while in the postabsorptive state. At the time of catheterization all patients were in either functional Class III or IV (New York Heart Association Classification). Simultaneous pulmonary arterial and right ventricular pressure curves were recorded respectively by a No. 6 Lehman catheter and a No. 8 Brockenbrough transseptal catheter. Sufficient polyethylene tubing and electrical damping was used in the system to obtain reasonable control of high frequency artifacts but without producing undue damping of the pressure curves as judged visually from the record. When the two catheters were used simultaneously, pressures were recorded in a common cardiac chamber (right ventricle) to insure comparable dynamic responses of the strain gauges and fluid filled catheter manometer systems. Statham P23Db strain gauges were used for pressure recordings on a Waters-Conley Photographic Recorder. The zero reference point for all pressure recording was taken as the midthoracic level. Cardiac output was measured by the Fick principle. Right ventricular systolic mean pressure was determined by planimetry from 10 consecutive beats. All other mean pres-

From the Cardiovascular Research Laboratory, Department of Medicine, University of Wisconsin Medical School, Madison, Wis.
This work was supported in part by the National Institutes of Health, United States Public Health Service, National Heart Institute Grants HE 07734, HE 14, 39, HE 5364, and HE 5736, and the Wisconsin Heart Association.
Received for publication June 13, 1970.
Reprint requests to: Donald A. Spring, M.D., Cardiovascular Research Laboratory, Department of Medicine, University of Wisconsin Medical School, 1300 University Ave., Madison, Wis. 53706.
*Postdoctoral Fellow in Medicine.
**Professor of Medicine.

scribed Five cases occurred in Bantu and one in a colored patient. None of the recognized complications or malformations known to cause heart failure in tetralogy of Fallot were operative in our cases. The evidence suggests that the heart failure was the result of associated cardiomyopathy which is a common disease among the South African Bantu Systemic hypertension has previously been described as a cause of heart failure in tetralogy these cases occurred in Negroes and it is possible that their heart failure was also a result of congestive cardiomyopathy and that the hypertension was a manifestation of the increased systemic vascular resistance accompanying cardiac decompensation

We wish to thank the Medical Superintendent of *Groote Schuur Hospital for permission to publish* and the South African Medical Research Council and the Cape Town City Council for their financial support.

REFERENCES

1. Keith J D Rowe R. D and Vlad P Heart disease in infancy and childhood ed 2 New York 1967 The Macmillan Company p. 608.
2. Nadas, A. S and Hauck A. J Pediatric *aspects of congestive heart failure Circulation* 21:424 1960.
3. Bonham Carter R. E. Anaemia in the tetralogy of Fallot. Symposium on congenital heart disease *Brit Heart J* 20:279 1958.
4. Holladay W E Jr., and Witham A. C.: Tetralogy of Fallot The variability of its clinical manifestations, Arch. Intern. Med. (Chicago) 100:400 1957
5. Nadas, A S. *Paediatric cardiology ed. 2* Philadelphia and London, 1963 W B Saunders Company p. 648.
6. Neufeld H N McGoon, D C DuShane J W and Edwards, J E. Tetralogy of Fallot with anomalous tricuspid valve simulating pulmonary stenosis, with intact septum Circulation 22:1083 1960
7. Kaplan S The effects of anaemia on the heart and circulation in paediatric cardiology London 1968 H Watson, Lloyd Luke p. 856.
8. Blumfield D K., and Liebman, J Idiopathic cardiomyopathy in children, Circulation 27:1071 1963
9. Schrire V The racial incidence of heart disease at Groote Schuur Hospital, Cape Town. Part III The less common forms of heart disease AMER. HEART J 59:835 1960.
10. Gillanders, A. D Nutritional heart disease, Brit Heart J 13:177 1951
11. Schwartz M B Schamroth, L., and Seftel, H. C. *The pattern of heart disease in the* urbanised (Johannesburg) African, Med. Proc. 4:275 1958.
12. Altman H and Stein, H: Idiopathic hypertrophy of the heart in African children, report *of four cases*, Brit. Med J 1:1207 1956.
13. Witham, A. C. Personal communication.

Table I. Summary of clinical and pathologic findings in five patients who had severe mitral insufficiency

Patient No., sex, age (yr.)	Etiology	Previous murmur	Duration symptoms	S_1	P_2	S_3	Murmurs	Cardio-thoracic ratio	ECG	Clinical Dx.	Pathologic findings
1 M, 61	RHD	Age 13	20 yr LHF RHF PND palp.	↑	↑ palp.	+	PSM 4/6 DR 2/6	58	A. Fib. No LVH	Sev. MI Sl. TI	Last 1/3 chordae ant. leaflet with rolled, thickened mitral valve
2 F, 61	?RHD	Age 15	1 yr LHF RHF PND	↓	S_2 single	+	PSM 5/6 DR 2/6	60	A. Fib. LVH	Sev. MI Sl. TI	—
3 F, 30	RHD	Age 9	20 yr LHF RHF PND	Variable	↑ palp.	—	PSM 3/6 DR 4/6 ASM 2/6 ADM	76	A. Fib. LVH	Sev. MI MS Sl. AS Sl. AI	Ca^{++} mitral leaf thickened chordae, rolled thickened leaflets mitral valve
4 F, 24	RHD	Age 13	3 yr LHF PND	—	↑ palp.	—	PSM 3/6 ASM ADM	67	NSR LVH	Sev. MI MS AI	Mitral valve edges thickened, rolled
5 M, 43	?RHD	0	4 mo. LHF RHF PND	Variable	↑ palp.	+	PSM 4/6	65	A. Fib. No LVH	Sev. MI	Torn chordae entire ant. leaflet mitral valve, bacterial endocarditis

A late systolic pressure wave was present in the pulmonary artery tracing of all patients. Patients 1 and 2 had evidence of premature closure of the pulmonary valve.
RHD = Rheumatic heart disease; LHF = left heart failure; RHF = right heart failure; PND = paroxysmal nocturnal dyspnea; palp = palpable; S_1 = apical first sound; P_2 = pulmonary closure sound; S_3 = diastolic filling sound; PSM = pansystolic murmur of apex; DR = diastolic rumble at apex; ASM = aortic systolic murmur; ADM = aortic diastolic murmur; LVH = left ventricular hypertrophy; A. Fib. = atrial fibrillation; NSR = normal sinus rhythm; MI = mitral insufficiency; MS = mitral stenosis; AI = aortic insufficiency; AS = aortic stenosis; TI = tricuspid insufficiency; Sev. = severe; and Sl. = slight.

occurred after the right ventricular systolic wave and in these subjects the pressure tracings were similar in form (Patient 5, Fig. 1, right panel). In the two subjects whose regurgitant wave was the *highest* (Patients 1 and 2), the upstroke of this abnormal wave began while the *right ventricle* was still in systole (Figs. 1 and 3, left panels). The total *pulmonary resistance* was increased in all subjects while pulmonary arteriolar resistance was normal in Patients 1, 3, and 5 and somewhat elevated in Patients 2 and 4 (Table II). One subject was recatheterized after replacement of the *mitral* valve with a prosthesis (Patient 1, Table II). The left atrial and pulmonary artery pressures were *within* normal limits, and there was no "V" wave. The pulmonary arterial pressure no longer exceeded that in the right ventricle and the abnormal late wave was no longer present in the pulmonary artery pressure record (Table II and Fig. 3, right panel).

In comparison, a study of the *hemodynamic* records of five subjects who had severe mitral insufficiency as the dominant lesion but who did not exhibit the late regurgitant wave in the pulmonary artery and of five subjects with trivial mitral

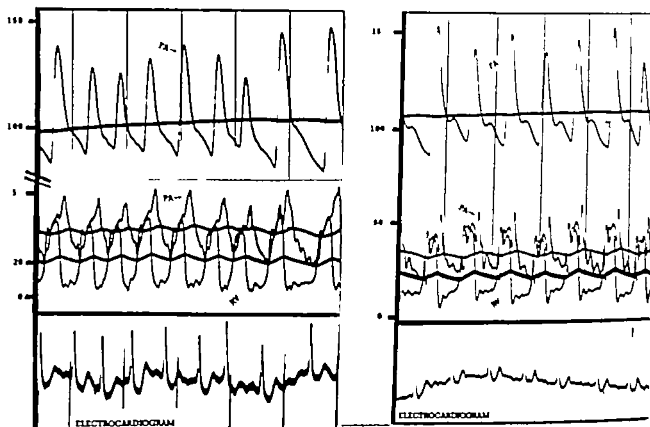


Fig 1 Simultaneous recordings of pulmonary rtery and right ventricular pressures. Premature closure of the pulmonary valve is seen in the traci g on the left (Patient 2) note the h gh late systolic pressure wave in the pulmonary artery (*PA*) which exceeds right ventricular pressure (*RV*) in midsystole. The tracing on the right (Patient 5) also show the late systolic pres ure wave characteristic of backward transmission of the left atrial V wave n this tracing, the late wave upstroke appears after the right ventricular systolic wave. *FA* = Femoral artery

sures were obtained by electrical damping through slow period galvanometers. Indicator dilution curves were recorded using indocyanine green dye and a cuvette densitometer

The hemodynamic findings in two additional groups of patients were analyzed for comparison with the reported cases the first group consisted of five patients having severe mitral insufficiency and the second group consisted of five patients who had mild mitral insufficiency in conjunction with a major lesion of another valve The severity of mitral insufficiency was judged on the basis of clinical examination as well as on the appearance of indicator in the left atrium after its injection into the left ventricle and on the amount of regurgitation seen during left ventriculography

Results

The clinical hemodynamic and anatomic findings in these subjects are summarized in Tables I and II and Figs. 1 to 3 Anatomic findings were obtained at autopsy or at the time of surgery in four of the five subjects (Table I)

Phonocardiographic studies performed in Patients 1 2 and 5 confirmed the clinical findings Patient 1 had a prominent outward precordial movement over the right ventricle synchronous with the pulmonary closure sound (Fig 2 left panel) The wave was not present after replacement of the mitral valve with a prosthesis (Fig 2 right panel) Cardiac catheterization revealed low cardiac indices, high left atrial V waves elevated left atrial mean pressures, and increased left ventricular end-diastolic pressure as summarized in Table II In all cases the mean pulmonary artery pressure exceeded the right ventricular systolic mean pressure and a high late regurgitant wave was seen in the pulmonary artery pressure curve In three subjects (Patients 3 4 and 5 Table II) the upstroke of the late wave

Table I Summary of clinical and pathologic findings in five patients who had severe mitral insufficiency

Patient Sex, age (yr.)	Etiology	Previous murmur	Duration symptoms	S_1	S_2P	S_3	Murmurs	Cardiothoracic ratio	ECG	Clinical Dx	Pathologic findings
1 M, 41	RHD	Age 15	20 yr LHF RHF PND palp.	↑	↑ palp.	+	PSM 4/6 DR 3/6	56	A. Fib. K LVH	Sev MI Sl. TI	Lost 1/3 chordae ant. leaflet with rolled, thickened mitral valve
2 F 61	?RHD	Age 13	1 yr LHF RHF PND	↓	S_2 single	+	PSM 4/6 DR 3/6	59	A Fib. LVH	Sev MI Sl. TI	—
3 F 30	RHD	Age 8	20 yr LHF RHF PND	Variable	↑ palp.	—	PSM 3/6 DR 4/6 ASM 2/6 ADM	76	A Fib LVH	Sev MI MS Sl. AS Sl. AI	Ca^{++} mitral leaf thickened chordae, rolled thickened leaflets mitral valve
4 F 24	RHD	Age 13	2 yr LHF PND	—	↑ palp.	—	PSM 3/6 ASM ADM	67	RSR LVH	Sev MI MS AI	Mitral valve edges thickened, rolled
5 M, 43	?RHD	0	4 mo. LHF RHF PND	Variable	↑ palp.	+	PSM 4/6	66	A. Fib. K LVH	Sev MI	Torn chordae on the ant. leaflet mitral valve verrucous endocarditis

A late systolic pressure wave was present in the pulmonary artery tracing of all patients. Patients and had evidence of premature closure of the pulmonary valve.

RHD = Rheumatic heart disease; LHF = left heart failure; RHF = right heart failure; PND = paroxysmal nocturnal dyspnea; palp. = palpable; S_1 = apical first sound; S_2P = pulmonary closure sound; S_3 = diastolic filling sound; PSM = pansystolic murmur of apex; DR = diastolic rumble at apex; ASM = aortic systolic murmur; ADM = aortic diastolic murmur; LVH = left ventricular hypertrophy; A. Fib = atrial fibrillation; RSR = regular sinus rhythm; MI = mitral insufficiency; MS = mitral stenosis; AI = aortic insufficiency; AS = aortic stenosis; TI = tricuspid insufficiency; Sev. = severe; and Sl. = slight.

occurred after the right ventricular systolic wave, and in these subjects the pressure tracings were similar in form (Patient 5 Fig 1 right panel) In the two subjects whose regurgitant wave was the highest (Patients 1 and 2) the upstroke of this abnormal wave began while the right ventricle was still in systole (Figs. 1 and 3 left panels) The total pulmonary resistance was increased in all subjects, while pulmonary arteriolar resistance was normal in Patients 1 3 and 5 and somewhat elevated in Patients 2 and 4 (Table II) One subject was recatheterized after replacement of the mitral valve with a prosthesis (Patient 1 Table II) The left atrial and pulmonary artery pressures were within normal limits and there was no "V" wave. The pulmonary arterial pressure no longer exceeded that in the right ventricle, and the abnormal late wave was no longer present in the pulmonary artery pressure record (Table II and Fig 3 right panel)

In comparison a study of the hemodynamic records of five subjects who had severe mitral insufficiency as the dominant lesion but who did not exhibit the late regurgitant wave in the pulmonary artery and of five subjects with trivial mitral

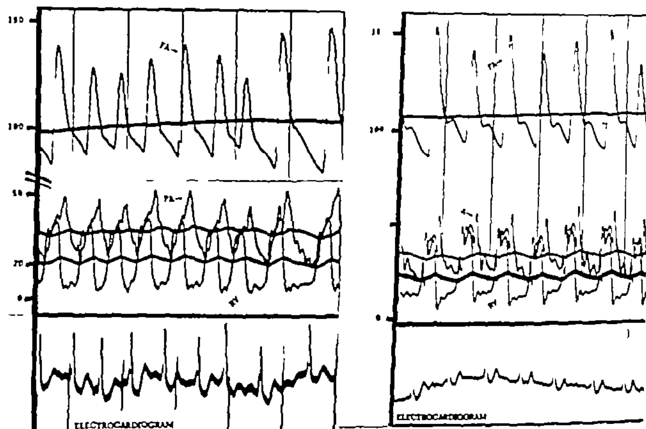


Fig. 1. Simultaneous recordings of pulmonary artery and right ventricular pressures. Premature closure of the pulmonary valve is seen in the tracing on the left (Patient 2): note the high late systolic pressure wave in the *pulmonary artery (PA)* which exceeds right ventricular pressure (*RV*) in midsystole. The tracing on the right (*Patient 5*) also shows the late systolic pressure wave characteristic of backward transmission of the left atrial V wave. In this tracing the late wave upstroke appears after the right ventricular systolic wave. *FA* = Femoral artery.

sures were obtained by electrical damping through slow period galvanometers. Indicator dilution curves were recorded using indocyanine green dye and a cuvette densitometer.

The hemodynamic findings in two additional groups of patients were analyzed for comparison with the reported cases: the first group consisted of five patients having severe mitral insufficiency, and the second group consisted of five patients who had mild mitral insufficiency in conjunction with a major lesion of another valve. The severity of mitral insufficiency was judged on the basis of clinical examination as well as on the appearance of indicator in the left atrium after its injection into the left ventricle and on the amount of regurgitation seen during left ventriculography.

Results

The clinical, hemodynamic, and anatomic findings in these subjects are summarized in Tables I and II and Figs. 1 to 3. Anatomic findings were obtained at autopsy or at the time of surgery in four of the five subjects (Table I).

Phonocardiographic studies performed in Patients 1, 2, and 5 confirmed the clinical findings. Patient 1 had a prominent outward precordial movement over the right ventricle synchronous with the pulmonary closure sound (Fig. 2, left panel). The wave was not present after replacement of the mitral valve with a prosthesis (Fig. 2, right panel). Cardiac catheterization revealed low cardiac indices, high left atrial V waves, elevated left atrial mean pressures, and increased left ventricular end-diastolic pressure as summarized in Table II. In all cases the mean pulmonary artery pressure exceeded the right ventricular systolic mean pressure and a high late regurgitant wave was seen in the pulmonary artery pressure curve. In three subjects (Patients 3, 4, and 5, Table II), the upstroke of the late wave

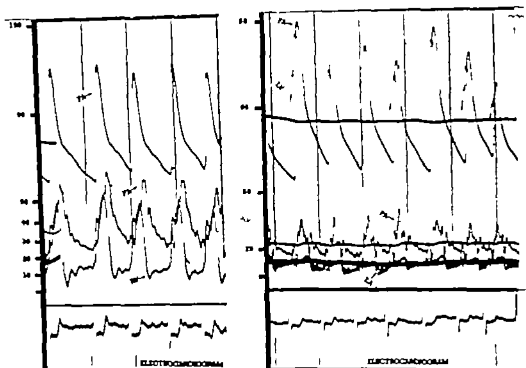


Fig. 3 Pre- and postoperative pressure recordings in Patient 1 The left panel, taken preoperatively shows premature closure of the pulmonary valve the late systolic pressure av of the pulmonary artery (*PA*) exceeds the right ventricular systolic wave (*RV*) beginning t peak systole. The right panel shows the pulmonary artery pressure returned t normal levels, and absence of the lat systolic pressure ve after prosthetic replacement of the mitral val *FA* = Femoral artery

and decreased compliance at higher pressures, especially over 25 mm Hg A marked reduction in the vascular compliance and a greatly diminished coefficient of elasticity of the main pulmonary artery has been found in human subjects with pulmonary hypertension [12] Considerably ncreased forward and particularly backward transmission of pressure waves were reported in the pulmonary circuit of two subjects w th pulmonary hypertension [13] and t was suggested that increased retrograde transmission of a pressure wave may ndicate reduced pulmonary arterial compliance Thus, in some cases of marked mitral regurgitation w th pulmonary arterial and venous hypertension, a reduction in pulmonary vascular compliance would be expected to result n enhanced transmission of left atrial pressure into the pulmonary artery

It has also been suggested that a normal pulmonary arteriolar resistance is required for retrograde transmission of the regurgitant pressure wave through the vessels of the lung and that increased arteriolar resistance would have an attenuating effect. In support of this, pulmonary arteriolar resistance was found to be normal in subjects with severe mitral insufficiency who manifested the late regurgitant pressure wave in the pulmonary artery pressure pulse[3] and was normal in three of our subjects (Table II)

The absence of regurgitant pressure waves in the pulmonary arterial pressure tracings of the group of subjects having closely similar peak V wave pressures in the left atrium (Table III) may be due to less marked pressure changes in the left atrium produced by mitral regurgitation Thus, in the group of subjects with the late regurgitant pressure wave in the pulmonary artery the base to-peak height of the left atrial V wave averaged 32 mm Hg while in the group with no regurgitant

Table III Comparison hemodynamics

Patients	CI	LAMP†	LAV	RVSM	PAMP	PAR‡	TPuR	Angio	Ind dil	Dx
Studied patients	2 493	25	55	31	36	247	770	Sev MI	Sev MI	Sev MI
5 patients Sev MI	2 730	33	50	39	39	146	685	Sev MI	Sev MI	Sev MI
5 patients Mild MI	3 190	29	36	35	33	103	485	Mild MI	Mild MI	Mild MI

Table I comparison of hemodynamic findings between the reported group which had the late systolic wave in the pulmonary artery pressure pulse (studied cases) group of 5 patients having similar severity of mitral insufficiency but no late wave ("5 cases of severe MI") and group of 5 patients with mild mitral insufficiency ("5 cases of mild MI") Premature closure of the pulmonary valve was found in of the patients who had late systolic pressure ("studied cases")

LAMP = Left atrial mean pressure; LAV = left atrial "V" wave RVSM = right ventricular systolic mean pressure; PAMP = pulmonary artery mean pressure PAR = pulmonary arteriolar resistance and TPuR = total pulmonary resistance

*CI = Cardiac index L min /M

†All pressures expressed in mm Hg.

‡All resistances expressed in

artery pressure curve[2] Subsequent studies of human subjects with severe mitral insufficiency have revealed a similar late systolic shoulder or reflected wave in the pulmonary artery pressure curve[3-4] and our studies confirm these observations. However in none of the previous studies has the pulmonary artery pressure been reported to exceed the right ventricular systolic ejection pressure

Although early or premature closure of the mitral valve has been deduced to occur as a result of the diastolic reversal of pressure gradient between the left atrium and ventricle in severe aortic insufficiency[5,6] and mitral insufficiency[7] to our knowledge early closure of the pulmonary valve has not been reported It seems likely that the phenomenon has not been considered before since it is uncommon to record right ventricular and pulmonary arterial pressures simultaneously whereas it is common to record left atrial and left ventricular pressure simultaneously and thus to be aware of the pressure gradient at the mitral valve In the present study analysis of the pressure curves of subjects with severe mitral insufficiency and premature pulmonary valve closure revealed (1) a high left atrial V wave which exceeded the right ventricular and pulmonary artery systolic pressure (Patients 1 and 2 Table II) (2) reversal of the mean pressure gradient between the right ventricle and pulmonary artery so that pulmonary arterial mean pressure exceeded right ventricular systolic mean pressure (Table II) (3) a sharply inscribed late pressure peak in the pulmonary artery which was equal to or exceeded the right ventricular systolic pressure and (4) during pressure recording as a catheter was withdrawn from the pulmonary artery to the right ventricle the late pressure wave present in the pulmonary artery disappeared apparently cut off by the pulmonary valve

The reversal of the normal mean pressure relationships between the right ventricle and pulmonary artery coupled with the continuing rise in pulmonary artery pressure after both ventricles have stopped contracting supports the concept that regurgitation from the left ventricle may cause reversal of flow through the pulmonary circuit resulting in premature closure of the pulmonary valve and further diastolic elevation of pressure in the pulmonary artery

In the mechanism of production of the high regurgitant pressure wave the compliance of the pulmonary vascular bed must be considered Studies of pressure-volume relationships of the pulmonary vascular bed of the rabbit[9] and dog[10] reveal a progressive loss of distensibility

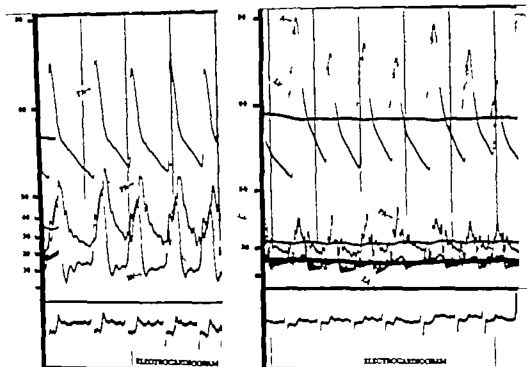


Fig. 3 Pre- and postoperative pressure recordings in Patient 1. The left panel, taken preoperatively, shows premature closure of the pulmonary valve; the late systolic pressure wave of the pulmonary artery (*PA*) exceeds the right ventricular systolic (*RV*) beginning at peak systole. The right panel shows the pulmonary artery pressure returned to normal levels, and absence of the late systolic pressure wave after prosthetic replacement of the mitral valve. *FA* = Femoral artery.

and decreased compliance at higher pressures, especially over 25 mm Hg. A marked reduction in the vascular compliance and a greatly diminished coefficient of elasticity of the main pulmonary artery has been found in human subjects with pulmonary hypertension.[23] Considerably increased forward and particularly backward transmission of pressure waves were reported in the pulmonary circuit of two subjects with pulmonary hypertension,[24] and it was suggested that increased retrograde transmission of a pressure wave may indicate reduced pulmonary arterial compliance. Thus, in some cases of marked mitral regurgitation with pulmonary arterial and venous hypertension a reduction in pulmonary vascular compliance would be expected to result in enhanced transmission of left atrial pressure into the pulmonary artery.

It has also been suggested that a normal pulmonary arteriolar resistance is required for retrograde transmission of the regurgitant pressure wave through the vessels of the lung and that increased arteriolar resistance would have an attenuating effect. In support of this, pulmonary arteriolar resistance was found to be normal in subjects with severe mitral insufficiency who manifested the late regurgitant pressure wave in the pulmonary artery pressure pulse[4] and was normal in three of our subjects (Table II).

The absence of regurgitant pressure waves in the pulmonary arterial pressure tracings of the group of subjects having closely similar peak V wave pressures in the left atrium (Table III) may be due to less marked pressure changes in the left atrium produced by mitral regurgitation. Thus, in the group of subjects with the late regurgitant pressure wave in the pulmonary artery, the base-to-peak height of the left atrial V wave averaged 32 mm Hg, while in the group with no regurgitant

waves in the pulmonary artery the corresponding average measurement was 21 mm Hg This difference is due to the lower average left atrial mean pressure the lower left ventricular and left atrial end-diastolic pressure and the slightly higher left atrial V wave in the group with the regurgitant wave (Table III) Therefore a more marked change in left atrial pressure was produced in the face of lower filling pressures Such a result can occur only under limited conditions either the volume of regurgitation is larger the rate of volume change more rapid (possibly reflecting better ventricular function) or the left atrial pulmonary vascular compliance is less The mean pulmonary artery pressures were comparable and there were no significant differences in pulmonary resistance between the two groups, while mean pulmonary venous pressure was clearly less in those with the large regurgitant wave in the pulmonary artery Thus it is unlikely that the striking difference in pulmonary artery pulse contour is due entirely to decreased pulmonary vascular compliance leading to the enhancement of backward wave transmission[9,13] The most likely cause of the regurgitant V wave in the pulmonary artery then is that the mitral regurgitation is greater in either force or volume or both It is suggested therefore that early pulmonary valve closure occurs only in very severe mitral insufficiency

Summary

The concept that premature pulmonary valve closure may result from severe mitral insufficiency is presented Five patients with severe mitral valve insufficiency had pulmonary arterial mean pressure which exceeded simultaneously recorded right ventricular mean systolic pressure A high delayed pressure wave was present in the pulmonary artery of these subjects and in four subjects the pulmonary arterial pressure rose above the right ventricular pressure In two of the five the timing and morphology of this pressure wave were suggestive of early closure of the pulmonary valve by retrograde transmission of the left atrial V wave through the pulmonary vessels Catheterization revealed low cardiac indices marked left atrial systolic pressure elevation and elevated pulmonary artery pressure All subjects had high total pulmonary resistance while pulmonary arteriolar resistance was normal in three and only moderately elevated in two The respective roles played by pulmonary arteriolar resistance compliance of the left atrium and pulmonary vasculature the state of left ventricular function and amount of mitral regurgitation in the production of this phenomenon are discussed

REFERENCES

1 Spencer M P and Denison A B Jr Pulsatile blood flow in the vascular system, in Hamilton, W F and Dow P editors Handbook of physiology Section 2 Vol 2 Washington D C 1963 American Physiological Society p 839
2 MacCallum W G and McClure R D On the mechanical effects of experimental mitral stenosis and insufficiency Bull Hopkins Hosp 1 :260 1906
3 Auger L, and Wigle, E D Sudden severe mitral insufficiency Canad Med Ass J 96:1493 1967
4 Radner S Suprasternal pressure curves in mitral insufficiency Acta Med Scand 152:1 1955
5 Levinson D S Wilburne, M Meehan, J P and Shubin, H Evidence of retrograde transpulmonary propagation of the V (or regurgitant) wave in mitral insufficiency Amer J Cardiol 2:159 1958
6. Meadows, W R Van Praagh S Indreika, M and Sharp J T Premature mitral valve closure, Circulation 28:251 1963
7 Wigle, E D and Labrosse C J Sudden severe aortic insufficiency Circulation 32 708 1965
8 Oliver G C Jr Gazetopoulos, N and Deuchar D C Reversed mitral diastolic gradient in aortic incompetence Brit Heart J 29:239 1967
9 Caro C G and Saffman P G Extensibility of blood vessels in isolated rabbit lungs, J Physiol (London) 178 193 1965
10. Sarnoff S J and Berglund E Pressure volume characteristics and stress relaxation in pulmonary vascular bed of the dog Amer J Physiol 171:238 1952
11 Patel, D J deFreitas, F M and Fry D L Hydraulic input impedance to aorta and pulmonary artery in dogs, J Appl Physiol 18 134 1963
12 Greenfield J C and Griggs, D M Relation between pressure and diameter in main pulmonary artery of man, J Appl Physiol 18:557 1963
13 Caro, C G Harrison, G K and Mognoni P Pressure wave transmission in the human pulmonary circulation, Cardiovasc Res 1:91 1967

Roentgenographic re-examination of the internal anatomy of the Taussig Bing heart

Paul Hinkes M.D
Glenn C Rosenquist M.D
Robert I White Jr., M.D **
Baltimore Md

Since its original description in 1949 the Taussig Bing heart has been a source of controversy both as to its actual anatomy and its proper classification[1-4] in the spectrum of developmental defects. Taussig and Bing in their report stated that the pulmonary artery overrides the septum and received blood directly *from* the left ventricle Neufeld and associates[4] classified the Taussig Bing malformation as a type of double-outlet right ventricle without pulmonary stenosis (Type IIa) In this classification system Type II has a high ventricular septal defect, located above what the authors call the crista supraventricularis the letters a and b signify whether the defect is below the pulmonary valve or below both semilunar valves, respectively Lev and co-workers[2] stated that there are in fact four types of Taussig Bing malformations, differentiated by position of the pulmonary trunk right sided type without overriding pulmonary trunk, right-sided with overriding trunk, intermediate type with straddling trunk, and left-sided type. Lev and associates included the original Taussig Bing heart in the group of right-sided malformations with overriding pulmonary trunks. Van Praagh[3] in a reexamination of the original heart, stated that the pulmonary trunk overrides the septum but does not override the *left* ventricular cavity the heart is a "true double-outlet right ventricle"

In the present study a technique of radiopaque marking and roentgenographic examination was used to clarify internal anatomy of the original Taussig Bing heart.

Materials and methods

The original Taussig Bing heart (JHH No. 44 95 05 Autopsy No 21039) was examined with a modification of the double-contrast x-ray method first described by Wright and co-workers.[6] Because the ventricles, atria, and great vessels had been opened it was impossible to restore the original anatomy entirely However the septum outflow tracts, and valve rings were intact and quite adequate for this study Plastic-coated wire rings were sutured in place around the circumference of the semilunar and atrioventricular valves just above the annuli and the great vessels

From the Departments of Pediatrics and Radiology The Johns Hopkins Hospital, Baltimore, Md
This investigation was supported in part by United States Public Health Service Research Grant HE 901 1 from the National Heart Institute.
Received for publication July 11, 1970,
Reprint request to Dr Glenn C. Rosenquist, CMSC 6-12 The Johns Hopkins Hospital, Baltimore, Md. 21205.
*Dr Hinkes now at the Department of Pediatrics, University of Pittsburgh Children Hospital.
**Dr Rosenquist is the recipient of Career Development Award from the National Institutes of Health (K3HE 3007
***Dr White is Scholar in Radiological Research of the James Picker Foundation, NAS-NRC.

waves in the pulmonary artery the corresponding average measurement was 21 mm. Hg. This difference is due to the lower average left atrial mean pressure, the lower left ventricular and left atrial end-diastolic pressure, and the slightly higher left atrial V wave in the group with the regurgitant wave (Table III). Therefore, a more marked change in left atrial pressure was produced in the face of lower filling pressures. Such a result can occur only under limited conditions: either the volume of regurgitation is larger, the rate of volume change more rapid (possibly reflecting better ventricular function), or the left atrial-pulmonary vascular compliance is less. The mean pulmonary artery pressures were comparable and there were no significant differences in pulmonary resistance between the two groups, while mean pulmonary venous pressure was clearly less in those with the large regurgitant wave in the pulmonary artery. Thus, it is unlikely that the striking difference in pulmonary artery pulse contour is due entirely to decreased pulmonary vascular compliance leading to the enhancement of backward wave transmission.[5,13] The most likely cause of the regurgitant V wave in the pulmonary artery, then, is that the mitral regurgitation is greater in either force or volume or both. It is suggested, therefore, that early pulmonary valve closure occurs only in very severe mitral insufficiency.

Summary

The concept that premature pulmonary valve closure may result from severe mitral insufficiency is presented. Five patients with severe mitral valve insufficiency had pulmonary arterial mean pressure which exceeded simultaneously recorded right ventricular mean systolic pressure. A high delayed pressure wave was present in the pulmonary artery of these subjects, and in four subjects the pulmonary arterial pressure rose above the right ventricular pressure. In two of the five, the timing and morphology of this pressure wave were suggestive of early closure of the pulmonary valve by retrograde transmission of the left atrial V wave through the pulmonary vessels. Catheterization revealed low cardiac indices, marked left atrial systolic pressure elevation, and elevated pulmonary artery pressure. All subjects had high total pulmonary resistance, while pulmonary arteriolar resistance was normal in three and only moderately elevated in two. The respective roles played by pulmonary arteriolar resistance, compliance of the left atrium and pulmonary vasculature, the state of left ventricular function, and amount of mitral regurgitation in the production of this phenomenon are discussed.

REFERENCES

1. Spencer, M. P., and Denison, A. B., Jr.: Pulsatile blood flow in the vascular system, in Hamilton, W. F., and Dow, P., editors: Handbook of physiology, Section 2, Vol. 2, Washington, D. C., 1963, American Physiological Society, p. 839.
2. MacCallum, W. G., and McClure, R. D.: On the mechanical effects of experimental mitral stenosis and insufficiency, Bull. Hopkins Hosp. 1:260, 1906.
3. Auger, P., and Wigle, E. D.: Sudden severe mitral insufficiency, Canad. Med. Ass. J. 96:1493, 1967.
4. Radner, S.: Suprasternal pressure curves in mitral insufficiency, Acta Med. Scand. 152:1, 1955.
5. Levinson, D. S., Wilburne, M., Meehan, J. P., and Shubin, H.: Evidence of retrograde transpulmonary propagation of the V (or regurgitant) wave in mitral insufficiency, Amer. J. Cardiol. 2:159, 1958.
6. Meadows, W. R., Van Praagh, S., Indreika, M., and Sharp, J. T.: Premature mitral valve closure, Circulation 28:251, 1963.
7. Wigle, E. D., and Labrosse, C. J.: Sudden severe aortic insufficiency, Circulation 32:708, 1965.
8. Oliver, G. C., Jr., Gazetopoulos, N., and Deuchar, D. C.: Reversed mitral diastolic gradient in aortic incompetence, Brit. Heart J. 29:239, 1967.
9. Caro, C. G., and Saffman, P. G.: Extensibility of blood vessels in isolated rabbit lungs, J. Physiol. (London) 178:193, 1965.
10. Sarnoff, S. J., and Berglund, E.: Pressure-volume characteristics and stress relaxation in pulmonary vascular bed of the dog, Amer. J. Physiol. 171:238, 1952.
11. Patel, D. J., deFreitas, F. M., and Fry, D. L.: Hydraulic input impedance to aorta and pulmonary artery in dogs, J. Appl. Physiol. 18:134, 1963.
12. Greenfield, J. C., and Griggs, D. M.: Relation between pressure and diameter in main pulmonary artery of man, J. Appl. Physiol. 18:557, 1963.
13. Caro, C. G., Harrison, G. K., and Mognoni, P.: Pressure wave transmission in the human pulmonary circulation, Cardiovasc. Res. 1:91, 1967.

were closed with silk sutures. Plastic-coated wires were placed in the main-stem bronchi and bent to conform to the paths of the bronchi.

After the heart was dried with absorbent paper a contrast material consisting of Barosperse powder and water in a 7:3 mixture (v:v) was applied with a camel's hair brush to different parts of the ventricular septum and ventricular outflow tracts as specified in the captions to the figures. Two separate applications of the barium mixture were needed to achieve an adequate radiopaque coating of the internal structures. The heart and lungs were placed so that they were in the normal anatomic relationship to each other in each radiograph projection by holding the entire specimen steady in a hollowed-out foam rubber pad. The pad was placed over a standard non screen film in a cardboard holder* and the bronchi were used for orienting the specimen as in vivo to a conventional portable x-ray unit. Roentgenograms of the heart were obtained in the anteroposterior (AP) left lateral, and right anterior oblique (RAO) projections (Fig 1) and in the left anterior oblique (LAO) projection (Fig 3). A projection perpendicular to the plane of the atrioventricular valves was also obtained (Fig 2). The exposure factors were 50 to 60 kilovolts at 25 milliampere-seconds, with a tube-to-film distance of 30 inches.

Anatomic overriding of the pulmonary trunk was measured by extending lines on the radiographs flush with the right and left ventricular septal surfaces upward through the pulmonary annulus (Fig 3).

Results

The ventricular septal defect (VSD) in the original Taussig Bing heart is anteriorly placed under the pulmonary valve ring (Fig 1 *A* and *D*). The semilunar valve

*Kodak RP/R-2 X-omat film.

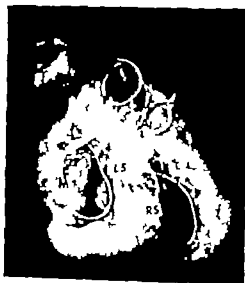


Fig. 2 Radiograph in projection perpendicular to plane of atrioventricular valves, showing relative positions of valves. Single radiopaque lines were painted opposite each other on the right and left ventricular septal walls from the crest of the septum to the apex, and on the ventricular walls opposite the septum.

rings appear side by-side in the AP view (Fig 1 *A*) and in the lateral view (Fig 1 *C*) they appear equally anterior. In both views the pulmonary valve ring appears slightly higher than the aortic valve ring and the semilunar valves are not in continuity with the atrioventricular valves (Fig 1 *A* and *C*). In radiographs taken perpendicular to the atrioventricular valves, the aortic valve is noted to be posterior to and to the right of the pulmonary valve (Fig 2).

The muscle band which separates aorta from pulmonary trunk (called the first parietal band by Lev and associates and the crista supraventricularis by Van Praagh[7]) is noted to deflect the subpulmonary portion of the right ventricle to the left (Fig 1 *A* and *B*).

Fig. 1 *A*, *B*, *C*, and *D* Radiographs and line drawings of the original Taussig Bing heart, showing relative positions of valves and ventricular septal defect. The right and left ventricular septal walls were painted with contrast material. *A* Anteroposterior (AP) projection. *B* Drawing of AP view made from stereoscopic films. *C*, Lateral projection. *D* Right anterior oblique projection. Abbreviations: *A* = Aortic valve ring; *B* = muscle band separating aorta from pulmonary trunk; *L* = left ventricular septal wall; *M* = mitral valve ring; *P* = pulmonary valve ring; *RS* = right ventricular septal wall; *T* = tricuspid valve ring; and *VSD* = ventricular septal defect.

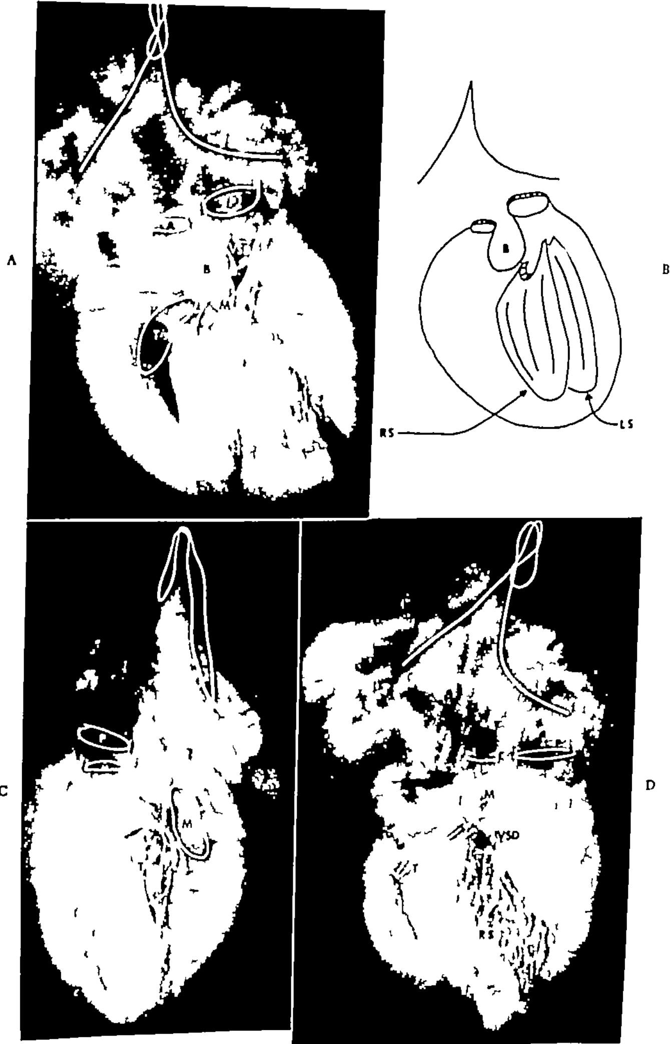


Fig. 1 For legend see opposite page.

ventricular septum and overrides both right and left ventricles. Lev's "intermediate type of Taussig Bing malformation"[3] seems to describe this heart most accurately

Discussion

The method of radiographic analysis presented in this study offers a valuable addition to pathologic study of cardiac malformations and permits definitive answers to such questions as valve positions and other anatomic relations. In intact heart specimens, a slightly more dilute paint (5.3 rather than 7.3) can be introduced into the heart chambers through thin plastic tubing threaded into the heart through the great veins or arteries. After the excess paint is drained from the specimen a thin layer is left coating the internal structures which provides excellent radiographic contrast. These methods not only produce a permanent stereoscopic picture of the internal anatomy but also avoid such problems as destruction of specimens in order to determine anatomy and distortion of anatomic relations. This latter problem almost inevitable whenever a heart is opened for inspection, can be avoided easily by this roentgenographic examination.

Summary

A modification of the Wright double-contrast x-ray technique was used to clarify the internal anatomy of the original Taussig Bing heart. The valves and ventricular outflow tracts were re-examined by marking internal structures with wires and radiopaque contrast material and then obtaining radiographs in standard and special views. These radiographs show valve positions and demonstrate that the pulmonary artery straddles the ventricular septal defect, and receives the outflow tracts of both left and right ventricles.

The authors wish to thank Dr Lora Teschkoff of the University of Washington for her consultation on the original double-contrast technique. We are also indebted to Dr Grover Hutchins of The Johns Hopkins Hospital Department of Pathology for lending his x-ray equipment and for reviewing this manuscript. W particularly wish to thank Dr Helen B. Taussig and Dr Maurice Lev for their reviews. Our thanks go also to Mrs. Soame Christianson for editing of the manuscript and to Mr Henri Hensels for technical assistance.

REFERENCES

1. Taussig H. B., and Bing R. J.: Complete transposition of the aorta and a levoposition of the pulmonary artery. AMER. HEART J 37:551, 1949
2. Van Praagh, R.: What is the Taussig Bing malformation? Circulation 38:445 1968.
3. Lev M Rimoldi, H. J A., Eckner F A. O., Melhuish, B. P Meng, L., and Paul, M. H.. The Taussig Bing heart: Qualitative and quantitative anatomy Arch. Path. 81:24, 1966.
4. Neufeld, H. N Lucas, R. V Lester R. G., Adams, P J Anderson, R. C., and Edwards, J E.. Origin of both great vessels from the right ventricle without pulmonary stenosis, Brit. Heart J 24:393, 1962.
5. Beuren, A.. Differential diagnosis of the Taussig-Bing heart from complete transposition of the great vessels with a posteriorly overriding pulmonary artery Circulation 21 1071 1960.
6. Wright, L. S Jaffe, R., Lewis, B. S., and Figley M. M: A method for double-contrast stereoscopic study of the internal anatomy of the heart, Radiology 83 1003 1964.

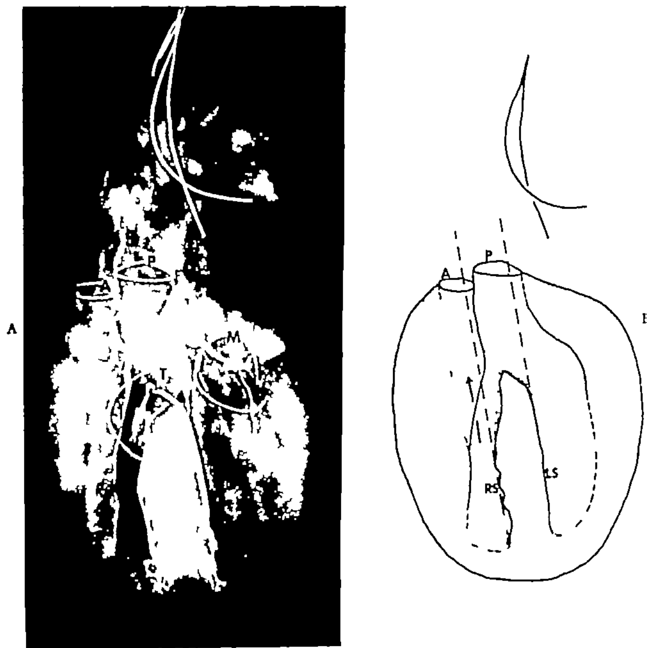


Fig 3 A and B Radiograph (left anterior oblique [LAO] projection) and line drawing illustrating the relationship of the pulmonary annulus to the ventricular septum Heart pa nted as in Fig 2 A LAO projection. B Drawing of LAO view arrow ind cates aortic outflow tract.

The ventricular septum is wide at the apex but narrows as it nears the ventricular septal defect Whether the pulmonary trunk overrides the left or right ventricle depends upon the definition of overriding that is used A straight metal rod placed flush against the septal wall of the left ventricle near the apex exits through the pulmonary trunk as shown in the radiograph (Fig 3 A) and the drawing (Fig 3 B) approximately 25 per cent of the pulmonary valve annulus extends to the left of the line paralleling the left ventricular septal surface On the other hand a rod placed against the septal wall of the right ventricle near the apex does not exit through the pulmonary trunk and a line extended toward the pulmonary valve from the right ventricular septal surface near the apex does not intersect the valve ring at all (Fig 3 B) Further if a line is drawn flush with the right or left ventricular septal wall near the VSD the pulmonary valve ring is seen to override both ventricles (Fig 3 B) Thus the pulmonary valve ring in the Taussig Bing heart straddles the

Table I

N	Patient	Age	Diagnosis	ECG	H V (msec.)
1	B E.	56	Unknown	RBBB	37
2	R. M	44	Unknown	RBBB	50
3	G K.	53	Cardiomyopathy	RBBB	29
4	G. K.	61	ASHD	RBBB	33
5	G B	56	ASHD	RBBB	45
6	C. P	61	ASHD	RBBB	40
7	J C.	55	Unknown	RBBB	52
8	M J	42	Unknown	LBBB	59
9	L. S.	66	HCVD	LBBB	59
10	E. K.	58	ASHD	LBBB	63
11	F M.	43	ASHD	LBBB	58
12	D B	62	ASHD	LBBB	68
13	S H.	64	ASHD	LBBB	54
14	L. S.	77	ASHD	LBBB	54
15	B K.	62	ASHD	LBBB	65
16	G R	70	Unknown	LBBB	66
17	M B	62	ASHD	RBBB LAD	56
18	W S.	56	ASHD	RBBB LAD	47
19	J B	81	ASHD	RBBB LAD	45
20	G H	70	Unknown	RBBB LAD	35
21	J L.	66	Unknown	RBBB LAD	38
22	R. R.	79	Unknown	RBBB LAD	42 55
23	S. S.	54	Unknown	Intermittent LBBB	26 43†
24	J C.	55	ASHD	Intermittent LBBB	45 55†
25	C B	62	ASHD	LBBB with 1° A-V block	111
26	T D	64	ASHD	LBBB with 1° A-V block	119

*During normal ventricular activation.
†During LBBB.

right bundle branch block (RBBB) six had RBBB and left axis deviation (LAD) eleven had left bundle branch block (LBBB) and two had intermittent LBBB Two of the patients with LBBB had prolonged P R intervals, whereas the remainder of the patients had P R intervals of less than 0 20 seconds. Using local anesthesia a tripolar electrode catheter* was percutaneously introduced into the right femoral vein and fluoroscopically positioned across the tricuspid valve. The proximal terminals of the electrodes were connected to a distribution switch box* from which simultaneous bipolar leads could be obtained Each bipolar lead was connected to the A-C input of an electrocardiogram (ECG) preamplifier The filter frequencies of the ECG amplifiers were set at 40 and 500 c.p.s. A standard ECG lead was simultaneously monitored and recorded. The electrode catheter was withdrawn slowly across the tricuspid valve until a rapid biphasic or triphasic deflec

*United States Catheter Corporation, Glens Falls, N. Y

*Electronics for Medicine, White Plains, N. Y

Experimental and laboratory reports

The use of His bundle recordings in the analysis of unilateral and bilateral bundle branch block

Walter D. Berkowitz, M.D.
Sun H. Lau, M.D.
Robert D. Patton, M.D.
Kenneth M. Rosen, M.D.
Anthony N. Damato, M.D.
Staten Island, N. Y.

The cardiac impulse, which is normally initiated in the sinoatrial node, traverses the atria, atrioventricular node, bundle of His, the bundle branches, and part of the Purkinje fibers before it reaches the ventricular muscle mass. Initial depolarization of the ventricular muscle mass occurs at the central portion of the septum where the bundle branches terminate. The septum is activated from both the left and right bundle branches, but activation of the left side occurs initially.[1,2]

The P-R interval represents the delay in transmission of the atrial impulse to the ventricular septum. Since the major delay occurs at the atrioventricular node, it has not been a useful tool for evaluating conduction delay in the common bundle and its branches. In contrast, the technique of recording His bundle electrograms[3] allows for a more precise measure of conduction time and conduction delay in the common bundle and its branches. The interval from the His bundle electrogram to the onset of ventricular depolarization (H-V) represents conduction time from the terminal portion of the common bundle down the left bundle branch until the onset of septal depolarization in patients with normal ventricular activation and in those with right bundle branch block. Contrariwise, in patients with left bundle branch block the H-V interval represents conduction time from the terminal portion of the common bundle down the right bundle branch until the onset of ventricular depolarization.

This study had a twofold purpose: First, to determine the range of the H-V interval in patients with either left or right bundle branch block and thereby obtain an estimate of conduction time down each bundle branch in man, a measurement heretofore unobtainable; second, to demonstrate the usefulness of His bundle recordings in determining conduction delay or blocked impulse transmission in the contralateral bundle branch in patients with either left or right bundle branch block.

Methods

Right heart catheterization was performed on 26 patients in the postabsorptive nonsedated state. Seven patients had

From the Cardiopulmonary Laboratory, United States Public Health Service Hospital, Staten Island, N. Y.
This work was supported in part by the Federal Health Programs Service, United States Public Health Service Project Py 70-1, National Institutes of Health Projects HE 11829, HE 12336, and National Aeronautic and Space Administration contract No. T 22416 (G).
Received for publication May 6, 1970.
Reprint requests to: Dr. Anthony N. Damato, Cardiopulmonary Laboratory, United States Public Health Service Hospital, Staten Island, N. Y. 10304.

Table I

N	*Patient*	*Age*	*Diagnosis*	*ECG*	*H V (msec.)*
1	B E.	56	Unknown	RBBB	37
2	R. M	44	Unknown	RBBB	30
3	G K.	53	Cardiomyopathy	RBBB	29
4	G. K.	61	ASHD	RBBB	33
5	G. B	56	ASHD	RBBB	45
6	C. P	61	ASHD	RBBB	40
7	J C.	55	Unknown	RBBB	52
8	M J	42	Unknown	LBBB	59
9	L. S.	66	HCVD	LBBB	59
10	E. K.	58	ASHD	LBBB	63
11	F M	43	ASHD	LBBB	58
12	D B	62	ASHD	LBBB	68
13	S H.	64	ASHD	LBBB	54
14	L. S.	77	ASHD	LBBB	54
15	B K.	62	ASHD	LBBB	65
16	G R.	70	Unknown	LBBB	66
17	M B	62	ASHD	RBBB LAD	56
18	W S.	56	ASHD	RBBB LAD	47
19	J B	81	ASHD	RBBB LAD	45
20	G H	70	Unknown	RBBB LAD	35
21	J L.	66	Unknown	RBBB LAD	38
22	R. R.	79	Unknown	RBBB LAD	42
23	S. S.	54	Unknown	RBBB LAD	55
24	J C.	55	ASHD	Intermittent LBBB	26 43†
25	C B	62	ASHD	Intermittent LBBB	45 55†
26	T D	64	ASHD	LBBB with 1 A-V block LBBB with 1 A V block	111 119

*During normal ventricular activation
†During LBBB.

right bundle branch block (RBBB) six had RBBB and left axis deviation (LAD) eleven had left bundle branch block (LBBB) and two had intermittent LBBB Two of the patients with LBBB had prolonged P R intervals, whereas the remainder of the patients had P R intervals of less than 0.20 seconds. Using local anesthesia, a tripolar electrode catheter* was percutaneously introduced into the right femoral vein and fluoroscopically positioned across the tricuspid valve The proximal terminals of the electrodes were connected to a distribution switch box* from which simultaneous bipolar leads could be obtained Each bipolar lead was connected to the A-C input of an electrocardiogram (ECG) preamplifier The filter frequencies of the ECG amplifiers were set at 40 and 500 c.p.s. A standard ECG lead was simultaneously monitored and recorded. The electrode catheter was with drawn slowly across the tricuspid valve until a rapid biphasic or triphasic deflec

*United States Catheter Corporation, Glens Falls, N. Y.

*Electronics for Medicine, White Plains, N. Y.

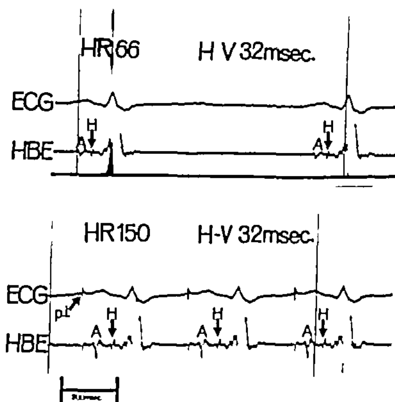


Fig 1 The effect of increasing the heart rate on the H V interval in a patient with right bundle branch block. At a sinus rate of 66/min (upper panel) the H V interval was 32 msec. At a paced atrial rate of 150/min (lower panel) the H V interval remains 32 msec A = Atrial electrogram H = His bundle electrogram V = ventricular electrogram pi = pacing impulse

tion appeared between the atrial and the ventricular electrogram and within the P R interval All records were made on a multichannel oscilloscopic photographic recorder† at paper speeds of 100 to 200 mm per second In most patients an additional bipolar catheter was percutaneously introduced into an antecubital vein and fluoroscopically positioned against the lateral wall of the right atrium This catheter was used to pace the right atrium up to 150 beats per minute Right atrial pacing was accomplished by using a battery powered pacemaker that delivered impulses of 2 msec duration at an adjusted milliamperage to insure reliable atrial capture Measurements were made of the interval from the P wave to the His bundle deflection (A H or P H interval) and from the His bundle deflection to the onset of the ventricular electrogram (H V interval) All equipment was carefully grounded

Results

The H V intervals of all the patients in this study are presented in Table I

RBBB In 7 patients with RBBB and normal P R intervals (<0 20 sec) the H V interval ranged from 37 to 52 msec and averaged 38 7 msec Of note in a group of 35 patients with normal ventricular activation studied in our laboratory the H V interval averaged 38 msec. Thus, there was no significant difference in conduction time from the His bundle electrogram to the onset of septal depolarization in normals and in patients with RBBB Increasing the heart rate by atrial pacing had no effect on the H V interval in patients with RBBB as demonstrated in Fig 1 In the top panel at a sinus rate of 66/min the H V interval was 32 msec. Increasing the heart rate to 150/min by atrial pacing did not alter the H V interval (bottom panel)

LBBB In 9 patients with LBBB and normal P R intervals the H V intervals ranged from 54 to 68 msec. (Table I) and averaged 60 msec Thus the average H V interval was 22 msec. longer in patients with LBBB as compared to those with RBBB Furthermore there was no overlap

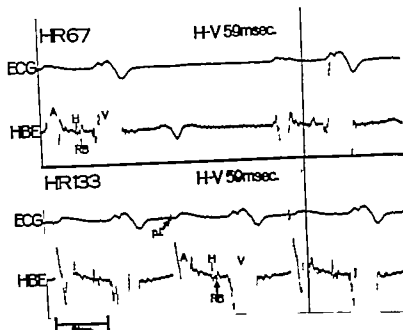


Fig. 2 The effect of increasing the heart rate on the H-V interval in patient with left bundle branch block (LBBB). At sinus rate of 67/min. (upper panel) the H-V interval as 59 msec. At paced atrial rate of 133/min. the H-V interval remains 59 msec. *RB* = Right bundle electrogram.

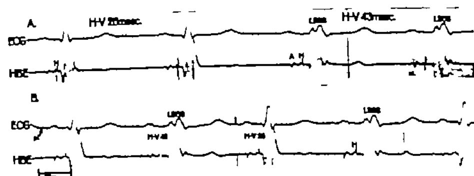


Fig. 3 The effects of intermittent or alternating left bundle branch block on the H-V interval. During regular sinus rhythm (panel *A*) the first two beats are conducted normally and the H-V interval is 26 msec. Without any change in heart rate LBBB pattern appears and the H-V interval is 43 msec. During fixed rate atrial pacing (panel *B*) 2:1 LBBB is present with alternation of normally conducted beats (H-V 26 msec.) and those with LBBB pattern (H-V 43 msec.)

in individual measurements between the two groups (Table I). Increasing the heart rate by atrial pacing had no effect on the H-V interval in patients with LBBB as demonstrated in Fig. 2. In the top panel during regular sinus rhythm the H-V interval was 59 msec. Increasing the heart rate by atrial pacing to 133/min. did not alter the H-V interval (bottom panel).

Intermittent LBBB. Two patients with an intermittent LBBB pattern were studied. The tracings of one of these patients are presented in Fig. 3. In panel *A* during regular sinus rhythm the first two beats are "normally" conducted whereas the last two beats have a LBBB pattern. This change in conduction is not rate related. The normally conducted beats have an H-V interval of 26 msec., whereas the beats with a LBBB pattern have an H-V interval of 43 msec. In the former instance septal depolarization occurred via the left

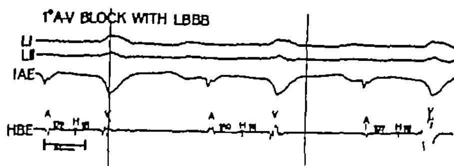


Fig 4 First degree A V block with LBBB The patient has a sinus arrhythmia with an A H interval varying between 172 and 197 msec and a prolonged H V interval of 111 msec indicating first degree block of the right bundle branch *LI* and *LII* are ECG leads *IAE* = Intra-atrial electrogram

bundle branch whereas in the latter it occurred via the right bundle branch Therefore conduction time down each bundle branch in this patient differed by 17 msec. Increasing the heart rate by atrial pacing induced alternation of normally conducted and LBBB beats (2 1 left bundle branch block) (panel *B*) with H V intervals of 26 and 43 msec respectively At higher paced rates all beats manifested a LBBB pattern In the other patient with intermittent LBBB the H V intervals of the normally conducted and LBBB beats were 45 and 55 msec respectively

RBBB with LAD In 6 patients with this pattern the H V interval ranged from 35 to 56 msec (Table I) and averaged 47 msec Four of the patients had H V intervals which overlapped those of patients with RBBB alone However two patients had H V intervals of 55 and 56 msec values exceeding those found in patients with RBBB alone suggesting the presence of conduction delay in the portion of the left bundle which activates the ventricular septum One of the two patients with a prolonged H V interval subsequently developed complete heart block requiring the insertion of a transvenous ventricular pacemaker

First degree A V block with bundle branch block The longest H V interval in 8 patients with LBBB and normal P R intervals was 68 msec. as shown in Table I In 2 patients with prolonged P R intervals and LBBB the H V intervals were 111 and 119 msec One of their tracings is presented in Fig 4 In this patient with a sinus arrhythmia and varying P R intervals the A H intervals varied between 172 and 197 msec and the H V interval was 111 msec. The A H intervals of 172 183 and 197 msec indicate delayed conduction at the level of the A V node * and the H V interval of 111 msec. indicates delayed conduction in the right bundle branch

Second degree A V block and bundle branch block Type I Wenckeback phenomenon Wenckebach phenomena did not occur spontaneously in any patient in this study However in several patients Type I A V block was induced by rapid atrial pacing In all instances the area of block was proximal to the His bundle presumably in the A V node. A representative tracing is presented in Fig 5

Type II second degree A V block Type II second degree A V block occurred spontaneously in two patients with LBBB and was induced by atrial pacing in a patient with RBBB and LAD In all instances the dropped beat was characterized by atrial depolarization followed by a His bundle recording but no ventricular depolarization indicating that the block in impulse transmission probably occurred in the contralateral bundle All three patients eventually developed complete heart block. A representative tracing is presented in Fig 6 In this patient with 2 1 A V block and LBBB every P wave is followed by a His bundle electrogram indicating that the cardiac impulse was blocked probably in the right bundle branch

High grade A V block with bundle branch

*If one accepts 0.2 sec. as the upper limit of normal for the P R interval and, since the shortest H V interval recorded in our laboratory was 26 msec., the upper limit for the P-H interval would be approximately 174 msec.

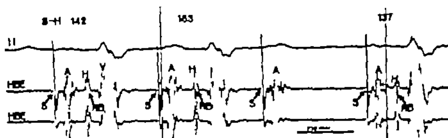


Fig. 5 An example of A-V nodal Wenckebach during atrial pacing in patient with LBBB. Top tracing is Lead II of the electrocardiogram. In the next two tracings *H* and *RB* potentials were recorded. *S* denotes stimulus artifact delivered to the right atrium. The S-H interval increases from 142 to 163 msec. The third atrial impulse is blocked proximal to the bundle of His. The cycle is repeated starting with the fourth atrial beat.

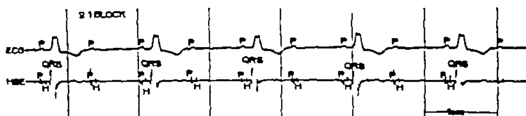


Fig. 6 Type II second degree A-V block in patient with left bundle branch block. The standard ECG lead shows 2:1 block with LBBB. The HBE reveals that the nonconducted P waves are blocked distal to the His bundle, indicating second degree block of the right bundle branch. This case was previously reported in Circulation 39:297 1969

block One patient with left bundle branch block developed 4:1 A-V block during rapid atrial pacing (Fig. 7). At a sinus rate of 82/min the P-H was 125 msec. and the H-V 59 msec. (upper panel). During atrial pacing at a rate of 150/min. the patient developed 4:1 A-V block (middle panel). This tracing demonstrates that during high grade A-V block the atrial impulses can penetrate into the A-V conducting system and can be blocked at varying levels. The first nonconducted atrial impulse (following the first QRS) was blocked distal to the His bundle recording whereas the subsequent two nonconducted beats were blocked proximal to the His bundle, presumably in the A-V node. At a paced rate of 140/min 2:1 A-V block was present (bottom panel). The first nonconducted atrial impulse was blocked proximal to the His bundle, however, the second nonconducted atrial impulse in the tracing penetrated into the right bundle branch before it was blocked.

Discussion

Activation of the ventricular septum occurs initially near its central portion where the bundle branches terminate. The majority of septal depolarization occurs from left to right, although a substantial portion of the septum is activated from the right side.[3] Amer and associates[1] noted in open-chested dogs that the time of earliest activation of the right and left sides of the septum differed by no more than one to two milliseconds in any animal with the left side always activated first. This study extends their observations to man. The H-V interval was used as an approximation of conduction time in the left bundle in patients with a right bundle branch block and in patients with normal QRS configurations. The H-V interval was used as a measure of right bundle conduction in patients with left bundle branch block.

The H-V intervals of patients with RBBB overlapped those of patients with

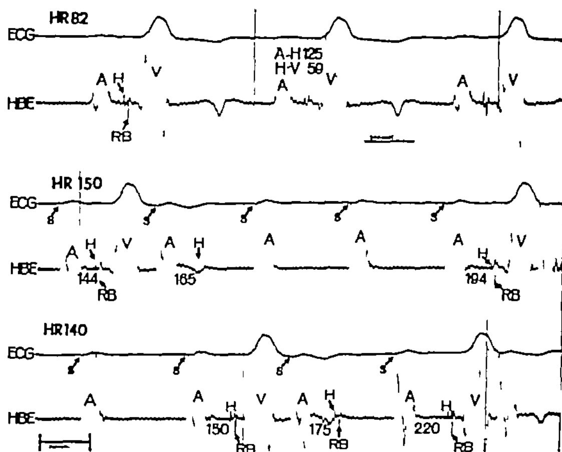


Fig. 7 High grade A V block induced by atrial pacing in a patient with left bundle branch block. In the upper panel during regular sinus rhythm 1 1 A V conduction is present. In the middle panel during atrial pacing (150/min.) 4 1 A V block is present. In the lowest panel during atrial pacing (140/min.) 2 1 A V block is present (see text for further details)

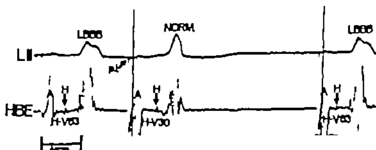


Fig. 8 The normalization of a LBBB pattern by premature atrial impulse. A premature atrial impulse results in a normalization of ventricular conduction. The H V interval of the normalized (Norm.) beat is 30 msec whereas that of the beats conducted with a LBBB pattern is 63 msec

normal QRS patterns. This finding suggests that there is no major change in the pathway which the cardiac impulse must traverse to initiate septal depolarization in patients with RBBB. These observations are in agreement with the findings of Rosenbaum and associates[4] and Cohen and co-workers[5] who used multiple ECG leads and planar vectorcardiograms to analyze the course of ventricular depolarization when premature atrial beats were conducted aberrantly. In 87 per cent of patients demonstrating an aberrant right bundle branch block pattern there was no change in the initial 0.02 to 0.04 sec vector.

In all instances the H V interval in patients with LBBB exceeded that of patients with RBBB. The average H V interval was 21 msec. longer in patients with LBBB as compared to RBBB. In this regard the two patients who manifested intermittent

left bundle branch block during the course of this study are of particular interest, since their changing pattern of ventricular depolarization presented a unique opportunity to obtain approximations of conduction time in each of their bundle branches. Their H V intervals during normal ventricular activation were 10 and 17 msec. shorter than when LBBB was present. The largest difference in left and right sided septal depolarization occurred in a patient with LBBB in whom the conduction abnormality normalized with application of premature atrial stimuli. Note in Fig. 8 that when the patient had a LBBB pattern the H V interval, representing conduction time in the right bundle branch, was 63 msec. With the application of a premature impulse, ventricular depolarization was normalized and the H V interval which represents conduction time in the left bundle branch was 30 msec. The ability of premature atrial stimuli to "normalize" bundle branch block patterns is a well recognized but poorly understood phenomena.[4-]

The differences in conduction time in each bundle branch may be due to differences in the length of the conduction pathway from the bifurcation of the common bundle to the points of insertion of the bundle branches into the septum and, or to differences in conduction velocity in each bundle branch.

Clinical and pathological studies have demonstrated that RBBB with LAD is a form of bilateral bundle branch block.[4-] The electrocardiographic pattern has been correlated with lesions of the anterior superior division of the left bundle and the second portion of the unarborized right bundle which run in close proximity to the anterior (superior) portion of the septum. Therefore in these patients, activation of the septum probably occurs primarily via the inferior posterior division of the left bundle branch. Scher[13] has reported that activation of the left septal mass occurs in two distinct areas almost simultaneously. These areas correspond to the terminal portions of the anterior superior and inferior-posterior divisions of the left bundle. Therefore, interruption of the anterior-superior division alone would not necessarily alter the onset of left septal depolarization. Thus, of the six patients in this study with RBBB and LAD four had H V intervals which overlapped those of patients with normal intraventricular conduction. However, two of the six patients with RBBB and LAD had prolonged H V intervals which suggest that they had more extensive lesions, involving either the left bundle proximal to its bifurcation or the inferior-posterior division, resulting in a decreased conduction velocity. In the study of Narula and co-workers[12] all six patients with RBBB and LAD (without previous myocardial infarction) had prolonged H V intervals. One of our patients with RBBB and LAD and a prolonged H V interval also manifested Type II second degree A V block, and eventually developed complete heart block. Thus, this patient represented one of the group of patients with RBBB and LAD (approximately 1[illegible] per cent in the study of Lasser and associates[14]) who eventually develop complete heart block. Prospective studies of a large group of patients with RBBB and LAD will be necessary to determine if and when a prolonged H V interval indicates impending complete heart block.

Scherf and Shookhoff[15] in a series of classic experiments sectioned one bundle branch and compressed the other and thereby produced various degrees of A V block, ranging from a prolonged P R interval to complete heart block. Subsequently Rosenbaum and Lepeschkin and Lenegre applied the concepts of first degree, second degree, and third degree block to the bundle branches in interpreting ECG's in which A V conduction disturbances were associated with a bundle branch block pattern. They emphasized that true bilateral bundle branch block must necessarily prolong or interrupt A V conduction. They suggested that when a prolonged P R interval with normal intraventricular conduction is associated at other times with a shorter P R interval and a bundle branch block pattern, the delay in A V conduction may be due to first degree block in the bundle branches. Similarly alternating right and left bundle branch block patterns with changing P R intervals on serial ECG's is diagnostic of

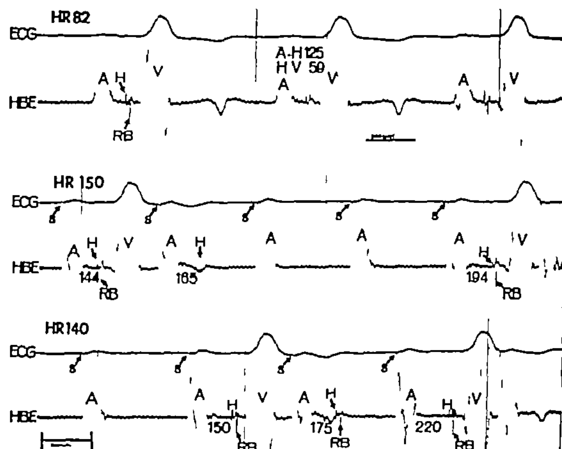


Fig. 7. High grade A-V block induced by atrial pacing in a patient with left bundle branch block. In the upper panel during regular sinus rhythm 1:1 A-V conduction is present. In the middle panel during atrial pacing (150/min.) 4:1 A-V block is present. In the lowest panel during atrial pacing (140/min.) 2:1 A-V block is present (see text for further detail.)

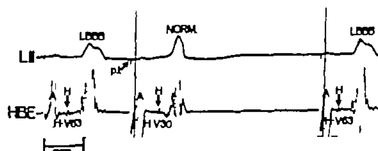


Fig. 8. The normalization of a LBBB pattern by a premature atrial impulse. A premature atrial impulse results in a normalization of ventricular conduction. The H-V interval of the normalized (Norm.) beat is 30 msec., whereas that of the beats conducted with a LBBB pattern is 63 msec.

normal QRS patterns. This finding suggests that there is no major change in the pathway which the cardiac impulse must traverse to initiate septal depolarization in patients with RBBB. These observations are in agreement with the findings of Rosenbaum and associates[4] and Cohen and co-workers[5] who used multiple ECG leads and planar vectorcardiograms to analyze the course of ventricular depolarization when premature atrial beats were conducted aberrantly. In 87 per cent of patients demonstrating an aberrant right bundle branch block pattern there was no change in the initial 0.02 to 0.04 sec. vector.

In all instances the H-V interval in patients with LBBB exceeded that of patients with RBBB. The average H-V interval was 21 msec. longer in patients with LBBB as compared to RBBB. In this regard the two patients who manifested intermittent

block. However His bundle electrograms have been recorded in over 100 patients in this laboratory and neither transient right bundle branch nor complete heart block has ever been induced

Summary

His bundle electrograms were recorded in 26 patients with bundle branch block. The interval from the His bundle electrogram to the onset of ventricular activation (H V) was used as an approximation of conduction time in the left bundle branch in patients with right bundle branch block and of conduction time in the right bundle branch in patients with left bundle branch block. The H V intervals of patients with right bundle branch block were within the range of those noted in patients with "normal" ventricular activation. The average H V interval of patients with left bundle branch block was 22 msec. longer than that of patients with right bundle branch block and there was no overlap of individual values. Two patients with alternating LBBB had shorter H V values during "normal" ventricular activation. Normalization of a bundle branch block pattern by premature atrial stimulation resulted in a shortening of the H V interval. Two of six patients with right bundle branch block and left axis deviation had prolonged H V intervals suggesting disease of either the most proximal portion of the left bundle branch or of the posterior inferior division. The longest H V values were observed in two patients with prolonged P R intervals and left bundle branch block suggesting delayed conduction in the right bundle branch. Type I second degree A V block induced by atrial pacing resulted in blocked impulse transmission proximal to the H potential. In Type II second degree A-V block the cardiac impulse was blocked distal to the H potential presumably in the contralateral bundle branch. Concealed conduction with blocked impulse transmission in the distal portion of the right bundle branch was observed

REFERENCES

1 Amer N S, Stuckey J H, Hoffman, B F, Cappelletti, R R and Domingo, R T Activation of the interventricular septal myocardium studied during cardiopulmonary bypass, Amer. Heart J 59:224, 1960.
2. Sodi-Pallares, D and Calder R. M. New basis of electrocardiography St. Louis, 1956, The C. V Mosby Company
3 Scherlag, B J Lau, S. H, Helfant, R. H, Berkowitz, W D Stein, E, and Damato, A. N Catheter technique for recording His bundle activity in man, Circulation 39 13 1969
4. Rosenbaum, M. B Elizari, M V and Lazzari, J O Los hemibloqueos, Buenos Aires, 1967 Ed. Paidos.
5. Cohen, S. I Lau, S. H, Stein, E, Young M W and Damato, A. N Variations of aberrant ventricular conduction in man Evidence of isolated block within the specialized conduction system. An electrocardiographic and vectorcardiographic study Circulation 38:899 1968.
6. Scherf D and Scherf M M Supernormal phase of intraventricular conduction, Amer Heart J 36:621 1949
7 Coutro, S Magri C and Natali, G. Premature beats overcoming impaired intraventricular conduction. Supernormal phase of intraventricular conduction, Amer. Heart J 81:378, 1956.
8. Schamroth, L. The supernormal phase of intraventricular conduction, Brit. Heart J 31:347 1969
9 Lenegre, J Etiology and pathology of bilateral bundle-branch block in relation to complete heart block, Progr Cardiovasc. Dis. 6:409 1964.
10. Lenegre, J Bilateral bundle branch block, Cardiologia 48 134, 1966.
11. Saltzman, P Linn, H and Pick, A. Right bundle-branch block with left axis deviation Brit. Heart J 28 703 1966.
12. Scher A. M The electrical correlation of the cardiac cycle, *in* Ruch, T C, and Fulton, J F., Medical physiology and biophysics, Philadelphia, 1960, W B. Saunders Company
13. Narula, O S., Lister J W Scherlag, B J and Samet, P Analysis of right bundle-branch block and left axis deviation by His bundle recordings, Circulation 40 153 1969 (Abst).
14 Lasser R. P Haft, J I and Friedberg, C. K. Relationship of right bundle-branch block and marked left axis deviation (with left parietal or periinfarction block) to complete heart block and syncope, Circulation 37:429 1968.
15 Scherf D., and Shookhoff C.: Reizleitungsstorungen im Bundel. II Mitteilung, Wien, Arch. Inn. Med 11:425 1925.
16. Rosenbaum, M. B and Lepeschkin, E. Bilateral bundle branch block, Amer. Heart J 50 38, 1955
17 Damato A. N Lau, S. H Helfant, R. H, Stein, E., Patton, R. D Scherlag, B. J and Berkowitz, W D : A study of heart block in man using His bundle recordings, Circulation 39:297 1969
18 Lau, S. H Damato, A. N and Berkowitz,

bilateral bundle branch block However when a bundle branch block pattern is associated with a prolonged P R interval and serial ECG s are unchanged the delay in A V conduction may be at the level of the A V node or in the contralateral bundle Our study demonstrates the usefulness of His bundle recordings in defining the region of delay Both patients with prolonged P R intervals and LBBB had conduction delay (first degree block) of the right bundle as manifested by prolonged H V times In addition one of the patients had a prolonged A H interval indicating concomitant delay at the A V node

Both types of second degree atrioventricular block can be associated with a bundle branch block pattern Type I which is characterized by progressive lengthening of the P R interval of successive beats until one atrial impulse is completely blocked (Wenckebach phenomenon) was readily induced in many patients in this study by rapid atrial pacing As in patients without bundle branch block [17] the delay in impulse conduction always occurred proximal to the His bundle recording presumably in the A V node. Type II second degree A V block the rare form which is characterized by constant P R intervals and a single atrial beat is blocked periodically without warning is associated with a bundle branch block pattern with rare exceptions All instances of Type II second degree A V block observed in this study were characterized by blocked impulse transmission distal to the His bundle recording indicating second degree block of the contralateral bundle [18]

Similarly both patients with alternating left bundle branch block (2 1 LBBB) were examples of second degree block of the left bundle branch However since their right bundle branch was functionally intact there was no interruption of A V conduction 2 1 bundle branch block is a rare phenomena [19] Type I second degree block (Wenckebach phenomenon) of one bundle branch is even rarer although Rosenbaum and associates[20] and Friedberg and Schamroth[21] have recently presented examples of this phenomenon

Langendorf[22] introduced the term concealed conduction into clinical cardiology to define the aftereffects of a cardiac impulse that incompletely penetrates the A V conducting system Recently using the technique of His bundle recordings examples of concealed conduction were presented with evidence that the nonconducted impulse penetrated into the A V node[23] or distal to the point of His bundle recording [24] Fig 7 presents an example wherein the nonconducted impulse penetrates into the right bundle branch where it is blocked In the top panel during regular sinus rhythm at a rate of 87/min with 1 1 ventricular response the P H and H Q intervals are 125 and 59 msec. respectively In the bottom panel during atrial pacing at 140/min there is a 2 1 ventricular response (70/min) The first nonconducted atrial impulse in the tracing is blocked proximal to the His bundle However the second nonconducted atrial impulse is blocked distal to the H and RB potentials (in the right bundle branch) and the I H interval of the subsequent conducted beat in prolonged (220 msec) Another example of concealed conduction is presented in the middle panel of Fig 7 where despite the presence of 4 1 A V block and a ventricular response of 38/min the conducted beat has a prolonged P H interval of 194 msec It should be noted that the first nonconducted atrial impulse penetrated deepest into the A V conducting system as evidenced by the His bundle potential which it evoked The next two nonconducted beats did not penetrate as deeply since they were not followed by His bundle potentials This tracing supports the hypothesis that in the presence of decremental conduction successive cardiac impulses penetrate less deeply into the A V conduction system [22]

This study has demonstrated the usefulness of His bundle recordings in analyzing A V conduction in patients with bundle branch block However it must be emphasized that the technique used in this study must be applied with great care to patients with left bundle branch block It has been repeatedly demonstrated that transient right bundle branch block occasionally lasting several hours can occur during right heart catheterization Therefore there is a risk of precipitating complete heart block in a patient with left bundle branch

Current dipole moment density of the heart

Joseph C. Solomon, M.S.
Ronald H. Selvester, M.D.
Downey, Calif.

A simulation of electrocardiographic data on the surface of the torso with a mathematical model should include the anatomic and physiologic factors in a direct way if the model is to have any interpretive value. Essentially these factors consist of knowledge of the current dipole moment per unit area of the depolarizing region, the pathway of ventricular depolarization, and volume conductor properties of the torso medium. Scher and Young[1] discuss these factors in more detail in their studies of the pathway of ventricular depolarization in laboratory animals. Our mathematical modeling efforts generally follow the same approach. The pathway of ventricular depolarization is simulated by a digital computer program that replicates Huygens' method of wave front construction in an isotropic medium. The volume conductor properties of the torso are approximated by a digital computer solution of the boundary value problem employing the method of Gelernter and Swihart.

This paper reports a mathematical attempt to model the current dipole moment per unit area associated with the region of heart muscle undergoing depolarization. Our approach is to estimate the current dipole moment per unit area, Φ. The estimate is determined from macroscopic quantities that can be measured by inserting bipolar electrodes that are large compared to microscopic or cellular dimensions into heart muscle undergoing depolarization. By statistically fitting an equation to a mean wave form, values of certain parameters are estimated and used to calculate an approximate value for Φ.

The subjects of concern in this paper are the macroscopic field variables, namely the electric field and current dipole moment per unit area associated with the activation region in cardiac muscle undergoing depolarization. Other investigators have mapped the pathway of excitation in the heart with multipoint electrodes and have discussed the characteristics of the propagating front.[4-7] In general, the active region appears to be a diffused front narrow by comparison with large surface dimensions. Where the voltage is measured with differential (bipolar) electrodes, muscle strip experiments show biphasic wave forms. These wave forms suggest a form that is given by a dipole layer. However, from our observations and others in the intact ventricles, the wave forms observed from bipolar pairs gave predominately monophasic wave forms.[1,4,8] It was obvious from the monophasic wave forms that any attempt to estimate the parameters in the equation

From the Medical Science Service, Rancho Los Amigos Hospital, Downey, Calif.
Received for publication May 11, 1970.
Reprint requests to: Joseph C. Solomon, Medical Science Service, Rancho Los Amigos Hospital, 7601 East Imperial Highway, Downey, Calif. 90242.

Vol. 81, No. 3, pp. 351-360, March, 1971

W D Second degree A V block Submitted for publication.

19 Vesell H and Levine J 2 1 Bundle-branch block. Classification with special reference to the critical heart rate, Amer J Cardiol 6:963 1960

20 Rosenbaum M B Nau G J Levi R. J Halpern S. M Elizari M V and Lazzar J O Wenckebach period in the bundle branches, Circulation 40:79 1969

21 Friedberg H D and Schamroth L. The Wenckebach phenomenon in left bundle branch block Amer J Cardiol. 24:591 1969

22 Langendorf R Concealed A V conduction The effect of blocked impulses on the formation and conduction of succeeding impulses, Amer Heart J 35:542 1948.

23 Lau S. H Damato, A N Berkowitz, W D and Patton R. D A study of atrioventricular conduction in atrial fibrillation and flutter in man using His bundle recordings, Circulation 40:71 1969

24 Damato A. N Lau S. H Patton, R. D Steiner C and Berkowitz, W D A study of atrioventricular conduction in man using premature atrial stimulation and His bundle recordings, Circulation 40:61 1969

25 Moe G K. Abildskov J A., and Mendez C. An experimental study of concealed conduction Amer. Heart J 6 :338 1964

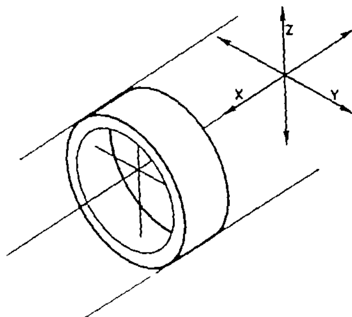


Fig 1 Center of the diffuse region lies on the Z Y plane and moving in the X direction. With the origin of the coordinates at the center of the distribution of dipole density and X the transverse direction, the right circular cylinder is an element of volume inside the diffuse region

position, whereas since there are only a finite number of current dipoles, the actual distribution is necessarily discontinuous. The distribution function cannot be interpreted when applied to a volume element so small that it contains only a few current dipoles.

Consider the origin of a coordinate system located at a point in the center of the active region which contains a total of N current dipoles. The orientation of this coordinate system reflects the symmetry of the active region. The geometry of the active region is of large surface dimensions compared to the thickness; therefore, the coordinate axes are chosen so that the Y and Z axes are in the plane of the surface and the X axis is perpendicular (Fig 1). Out of a total of N current dipoles, we first find what fraction has x components of position between some arbitrary value x and a slightly larger value $x + \delta x$. Referring to Fig 1 again, this fraction is the number of current dipoles in the thin slice of thickness δx and parallel to the Y Z plane. Letting $\delta N x$ represent the number in the slice, the fraction of the total number N of current dipoles lying in the slice is $\frac{\delta N x}{N}$. In general this fraction is a function of x; that is, it depends on where the slice is located and will be proportional to the thickness of the slice. If $n(x)$ is the density distribution of current dipoles in the x direction, then the fraction contained in the slice of thickness δx is $n(x)\ \delta x$. Equating these fractions, we obtain for the number of current dipoles in the slice,

$$\delta N x = N\ (x)\ \delta x \qquad (1)$$

To introduce the distribution functions along the Y and Z directions, it is necessary to consider some observations on the geometry of the pathway of ventricular depolarization. Studies of the pathway of ventricular depolarization with multichannel recording equipment have presented a three-dimensional view of the activating wave. This view suggests that the active region is conducted through the myocardium in a wave-front-like manner. If the active region is comprised of a large collection of current dipoles, then it seems certain their spatial distribution is directly related to the apparent net movement of the active region. We have chosen

for the potential difference produced by a dipole layer would result in failure Our solution to this problem assumes the active region to be a distribution of current dipoles presumably generated on a micro scopic level by the motion of charges across the membrane If it is assumed that the active region is a large collection of current dipoles distributed in some man ner throughout the region called the wave front the distribution function can then be postulated Our starting point for this postulate is based on the symmetry of the active region which is suggested by the results of activation studies in dogs and humans with multipoint bipolar elec trodes[1,7] This symmetry is regarded as a diffuse layer in the direction perpendicular to the direction of propagation The thick ness in the direction of propagation is small compared to the surface dimensions After postulating the distribution function the equations for the macroscopic electric field and current dipole moment per unit area can be derived The parameters of the field equations are estimated from the differential electrode measurements sub ject to constraints on the orientation of the electrodes relative to the wave front as pointed out by Scher Young Malmgren and Paton[4]

Since our objective is to model the electric field generated by the heart and relate it to the surface electrocardiograms we are not directly concerned about the nature or mechanisms occurring at the microscopic level The scope of this work does not extend beyond the assumption that the microscopic depolarization event can be represented as current dipoles In our overview of the microscopic current fields, no attempt is made to interpret or relate the results of this study to the mechanisms taking place at the cellular level neither is any attempt made to establish the existence of the current dipoles based on cellular mechanisms The sole intent is that the equations and results be interpreted as a mathematical model equivalent to the statistical re sultant of the cellular events over a region defined by the electrode size and separation

The first order of consideration is the distribution function for the current di poles based on a set of assumptions. From these assumptions the equations for the electric field and current dipole moment per unit area are derived The experimental results are used to evaluate the equation derived for the electric field The electric field equation is adjusted to the mean of the measured wave forms in the least squares sense Parameters representing the maximum electric field and approxi mate width of the activation region are calculated from this least-squares fitting procedure These parameters then are used to calculate the current dipole mo ment per unit area of the active region In addition an estimate of the electromotive force is given for a local region

Discussion of the model

In this discussion the activation front is considered a diffuse collection of a large number of current dipoles distributed spatially in the region undergoing de- polarization These current dipoles are assumed to arise from the depolarization of cells in which currents are generated over a short distance If we imagine the current to be represented by the letter i and the charges of this current flow across a directed line segment $\bar{l}$ then the current dipole will be $\bar{p} = i\bar{l}$ The reason for introducing the notion about current di poles is to establish the point of view to be taken regarding the underlying elec trical activity on a microscopic level to better define what we mean by a macro- scopic level A macroscopic dimension is small compared to the one millimeter electrodes used in our measurements, yet large compared to the length $\bar{l}$ of the cur rent dipole which might be on the order of the thickness of the cell membrane. The density of current dipoles in the activation region is considered sufficiently high that incremental dimensions still contain suf ficient quantities such as not to be dis- continuous. Any volume element must be large enough to contain a sufficient num ber of representative current dipoles, but small in comparison with the total di mensions of the active region These limi tations are imposed because we attempt to describe the current dipole moment distribution by a continuous function of

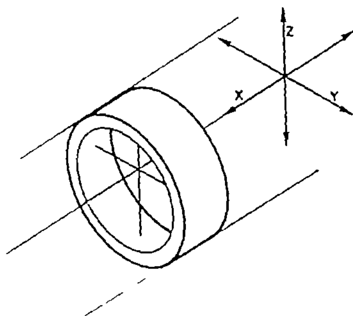


Fig 1 Center of the diffuse region lies on the Z-Y plane and moving in the X direction. With the origin of the coordinates at the center of the distribution of dipole density and X the transverse direction, the right circular cylinder is an element of volume inside the diffuse region

position, whereas since there are only a finite number of current dipoles, the actual distribution is necessarily discontinuous. The distribution function cannot be interpreted when applied to a volume element so small that it contains only a few current dipoles.

Consider the origin of a coordinate system located at a point in the center of the active region which contains a total of N current dipoles. The orientation of this coordinate system reflects the symmetry of the active region. The geometry of the active region is of large surface dimensions compared to the thickness; therefore, the coordinate axes are chosen so that the Y and Z axes are in the plane of the surface and the X axis is perpendicular (Fig. 1). Out of a total of N current dipoles, we first find what fraction has x components of position between some arbitrary value x and a slightly larger value $x + \delta x$. Referring to Fig 1 again, this fraction is the number of current dipoles in the thin slice of thickness δx and parallel to the Y Z plane. Letting δN_x represent the number in the slice, the fraction of the total number N of current dipoles lying in the slice is $\frac{\delta N_x}{N}$. In general this fraction is a function of x, that is, it depends on where the slice is located and will be proportional to the thickness of the slice. If n(x) is the density distribution of current dipoles in the x direction, then the fraction contained in the slice of thickness δx is $n(x)\ \delta x$. Equating these fractions, we obtain for the number of current dipoles in the slice

$$\delta N_x = N\ n(x)\ \delta x \qquad (1)$$

To introduce the distribution functions along the Y and Z directions, it is necessary to consider some observations on the geometry of the pathway of ventricular depolarization. Studies of the pathway of ventricular depolarization with multichannel recording equipment have presented a three-dimensional view of the activating wave. This view suggests that the active region is conducted through the myocardium in a wave-front like manner. If the active region is comprised of a large collection of current dipoles, then it seems certain their spatial distribution is directly related to the apparent net movement of the active region. We have chosen

for the potential difference produced by a dipole layer would result in failure Our solution to this problem assumes the active region to be a distribution of current dipoles presumably generated on a microscopic level by the motion of charges across the membrane If it is assumed that the active region is a large collection of current dipoles distributed in some manner throughout the region called the wave front the distribution function can then be postulated Our starting point for this postulate is based on the symmetry of the active region which is suggested by the results of activation studies in dogs and humans with multipoint bipolar electrodes[1,7] This symmetry is regarded as a diffuse layer in the direction perpendicular to the direction of propagation The thickness in the direction of propagation is small compared to the surface dimensions After postulating the distribution function the equations for the macroscopic electric field and current dipole moment per unit area can be derived The parameters of the field equations are estimated from the differential electrode measurements subject to constraints on the orientation of the electrodes relative to the wave front as pointed out by Scher Young Malmgren and Paton[4]

Since our objective is to model the electric field generated by the heart and relate it to the surface electrocardiograms we are not directly concerned about the nature or mechanisms occurring at the microscopic level The scope of this work does not extend beyond the assumption that the microscopic depolarization event can be represented as current dipoles In our overview of the microscopic current fields no attempt is made to interpret or relate the results of this study to the mechanisms taking place at the cellular level neither is any attempt made to establish the existence of the current dipoles based on cellular mechanisms. The sole intent is that the equations and results be interpreted as a mathematical model equivalent to the statistical resultant of the cellular events over a region defined by the electrode size and separation

The first order of consideration is the distribution function for the current dipoles based on a set of assumptions. From these assumptions the equations for the electric field and current dipole moment per unit area are derived The experimental results are used to evaluate the equation derived for the electric field The electric field equation is adjusted to the mean of the measured wave forms in the least squares sense Parameters representing the maximum electric field and approximate width of the activation region are calculated from this least-squares fitting procedure These parameters then are used to calculate the current dipole moment per unit area of the active region In addition an estimate of the electromotive force is given for a local region

Discussion of the model

In this discussion the activation front is considered a diffuse collection of a large number of current dipoles distributed spatially in the region undergoing depolarization These current dipoles are assumed to arise from the depolarization of cells in which currents are generated over a short distance If we imagine the current to be represented by the letter i and the charges of this current flow across a directed line segment $\overline{l}$ then the current dipole will be $\overline{p} = i\overline{l}$ The reason for introducing the notion about current dipoles is to establish the point of view to be taken regarding the underlying electrical activity on a microscopic level to better define what we mean by a macroscopic level A macroscopic dimension is small compared to the one millimeter electrodes used in our measurements, yet large compared to the length $\overline{l}$ of the current dipole which might be on the order of the thickness of the cell membrane The density of current dipoles in the activation region is considered sufficiently high that incremental dimensions still contain sufficient quantities such as not to be discontinuous. Any volume element must be large enough to contain a sufficient number of representative current dipoles, but small in comparison with the total dimensions of the active region These limitations are imposed because we attempt to describe the current dipole moment distribution by a continuous function of

The undetermined multiplier k can be expressed in terms of the separation (λ) between the maximum and minimum of ρ. After computing the extremums of Equation 10 the following expression for k is derived

$$k = \frac{4}{\lambda}$$

The current dipole moment per unit area of the active region in terms of E_m and the separation λ is then given by the integral

$$\Phi = \int^{\infty} \lambda_\rho \, dx$$

Evaluating the integral yields

$$\Phi = \epsilon_o \lambda E_m \qquad (11)$$

Equation 11 expresses the current sources and sinks in the active region as a macroscopic current dipole moment density. The parameters λ and E_m can be measured experimentally. ϵ_o is a physical constant equal to 8.864 × 10^{-12} coul² n M in the Giorgi system of units. From Ohm's law it is clear that E_m occurs where the current density is a maximum. λ represents the distance between the means of the current sources and sinks for a local region of the activation front.

The electromotive force across the active region is estimated by evaluating a line integral over the function E given in Equation 8. A closed path is formed on the interval $-\infty$ to $+\infty$. Results of the integration yield

$$EMF = \sqrt{\ /2}\, \lambda E_m \qquad (12)$$

Methods

Seven dogs each weighing approximately 40 pounds, were used in the experiment. Two were used in pilot studies to establish recording procedures and the experimental design. The results for the remaining five dogs are given in this study. A detailed analysis of the animal experiments was reported elsewhere.[2]

Pickup from the myocardium was accomplished by electrodes constructed in this laboratory by Pearson similar to those used by the Scher[4] and Durrer[11] groups and composed of a bundle of 15 stainless steel wires 0.003 inches in diameter. Each wire terminated at a point 1.0 mm from adjacent terminations. The voltage differences between the 14 adjacent pairs were fed into 14 differential, solid state portable preamplifiers, also designed in this laboratory. The differential impedance at the inputs was approximately 5 megohms. The common mode rejection was better than 80,000:1. The frequency response was 6 db down at 0.2 cycles per second. Most recordings were made with a preamplifier gain of 100. Each preamplified signal was fed "single ended" into an input of a 14 channel FM carrier tape recorder (Ampex FR 1300).

In all of the experiments reported here channel 1 (nearest the needle tip) was omitted and replaced at the preamplifier input with a reference electrode held constant during the entire recording sequence. This reference electrode was a pair of small stainless steel needle electrodes inserted into a convenient site of myocardium and sutured in place. Any change in the wave form from this electrode was reason to terminate the experiment.

Analysis both of waveform and timing was permitted by playing back from each channel a single action potential (one cardiac cycle) and the reference signal simultaneously on a Tektronix type 564 storage oscilloscope.

Data were taken from three areas of the left ventricle in each dog: the base, midregion, and apex. To study a section five needles were placed in the myocardium 5 mm. apart. Each needle extended through the myocardium into the cavity so that the outermost electrode (Number 15) was located just below the epicardial surface of the heart. The voltage differences then were recorded for each adjacent pair of electrodes. A reference channel was provided by a pair of electrodes located in the right ventricle near the base. Fig. 2 shows the locations of the needles and a detailed sequence of depolarization of a typical vertical section from apex to base. This detailed map of the activation sequence in a portion of the left ventricular wall was taken to verify that the path way of depolarization in the outer 4 mm is principally in the direction of the electrodes inserted perpendicular to the epicardium. The construction of isochronous planes is essential if the actual speed and

an asymmetrical distribution for current dipoles that corresponds to the wave-front-like movement and shape of the active region This choice assumes that the distribution in the direction of net movement represented by n(x) has a different functional form than the distribution g(r) which is perpendicular to the net movement The distribution g(r) is considered isotropic in the plane perpendicular to the direction of movement

Returning to Fig 1 let δN be the number of current dipoles in a cylinder defined by some arbitrary radius r and a slightly large radius $r + \delta r$ Then the fraction of the total number N of current dipoles in the cylinder will be $\frac{\delta N}{N}$ This fraction is proportional to the distribution g(r) δr hence

$$\delta N = N g(r)\, 2\pi r\, \delta r \qquad (2)$$

Let $\delta^2 N$ represent the number of current dipoles that are in the region between x and $x + \delta x$ as well as between r and $r + \delta r$ If the distribution g(r) is assumed uniform then the fraction $\frac{\delta^2 N}{\delta N}$ is equal to the fraction $\frac{\delta N}{N}$ and we obtain from Equations 1 and 2 the $\delta^2 N$

$$\delta^2 N_{xr} = N\, n(x)\, g(r)\, 2\pi r\, \delta r\, \delta_x \qquad (3)$$

The density of current dipoles in the ring defined by (r r + δr) and (x x + δx) is

$$\sigma = N\, n(x)\, g(\;) \qquad (4)$$

The density σ is the same at every point in the ring where

$$\psi^2 = x^2 + r^2 = constant$$

from the assumed isotropy of g(r)

Applying the method of undetermined multipliers to the total differential of σ viz.

$$d\sigma = \nabla\sigma \cdot d\vec{\psi}$$

where

$$d\vec{\psi} = dx\, \hat{i} + dr\, \hat{j}$$

subject to the constraint

$$\psi^2 = x^2 + r^2 = constant$$

we find the form of n(x) is given as

$$n(x) = n\;\; exp \frac{-kx^2}{2} \qquad (5)$$

where k is the undetermined multiplier and n is the maximum density at the center of the active region

A way of representing the polarization is to relate it to the average dipole moment by multiplying this average moment by the number of dipoles per unit volume.

$$\overline{P}(\overline{R}) = \sigma(\overline{R})\; \overline{p} \qquad (6)$$

The component of $P(\overline{R})$ along the x axis is obtained by combining Equations 4 5 and 6 and the result becomes

$$P = P\;\; exp \frac{-kx^2}{2} \qquad (7)$$

where P = N n g(r) p

The electric field arising from this component of the polarization can be estimated as the electric field produced in a permanently polarized slab where the thickness is small compared to the surface dimensions. The electric field in the slab is given as $E = -P/\epsilon$ in the transverse direction When approximating the geometry of the active region as a slab the estimate of the electric field becomes

$$E = E_o\; exp \frac{-kx^2}{2} \qquad (8)$$

where E is the maximum electric field at the center of the active region and in the transverse direction

Equation 8 will be evaluated from the standpoint of our experiments and analysis of data since multipolar electrodes inserted into the ventricular muscle during depolarization measure the mean electric field as the wave of excitation propagates past. When adjacent electrodes are recorded differentially the ratio of the potential difference to electrode separation is a measure of the mean electric field in the direction defined by the two electrodes. However we are interested in estimating the current dipole moment per unit area associated with the active region To obtain this estimate we introduce an equivalent polarization charge density related to E(x) namely

$$\rho = -\epsilon_o \nabla \cdot E \qquad (9)$$

Combining Equations 8 and 9 yields the following equation for ρ

$$\rho = \epsilon_o\, kx E_o\; exp \frac{-kx^2}{2} \qquad (10)$$

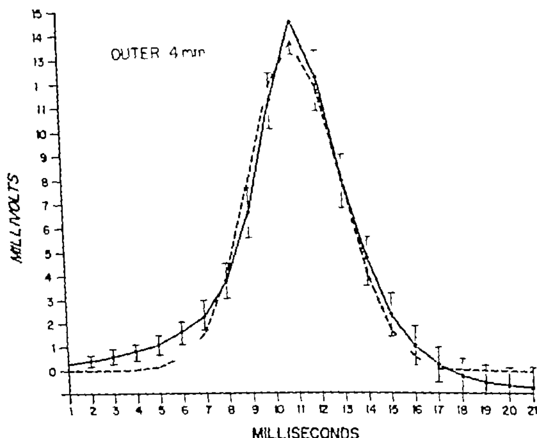


Fig. 3 Solid line represents the average of 222 wave forms recorded within the outer 4 mm. of the left ventricle in five dogs and with 95 per cent confidence intervals. The dashed line represents the least-squares fit of the derived electric field in the direction of the needles.

in milliseconds (t). Since the spacing was 1 mm the velocity is just t.

Results

The following are the results of fitting Equation 8 to the waveform data of the outer 4 millimeters of myocardium: maximum electric field E_m = 13.50 mv, λ = 1.5 mm, propagation rate = 40 cm. per second and the error-of-estimate chi-square test = 1.03.

The chi-square value for significance ($p < 0.01$) is approximately 1.3. Since the value 1.03 is less than this, the error-of-estimate and the data variability can be said to compare favorably.

Fig. 3 shows the mean wave form with 95 per cent confidence intervals along with the estimated function (Equation 8). The mean curve is given in the time domain since the data are taken in this manner. To present the spatial domain the millisecond values along the abscissa are multiplied by the propagation velocity as was done to obtain the value of λ for the model.

The estimated curve is consistently lower in value at the tails than the averaged waveform and suggests that the range of validity of the proposed distribution function does not extend beyond several millimeters from the center of the activation unless this deviation is the result of a phenomenon such as induced polarization currents.

The charge distribution equivalent to the current dipole distribution in the x direction, is given by Equation 10. This polarization charge distribution gives rise to the same electric field as the distributed

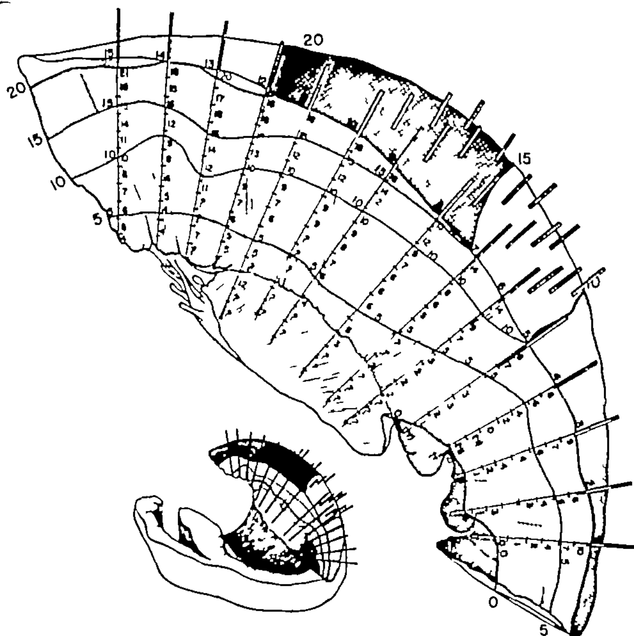


Fig 2 Detailed activation sequence in the free left ventricular wall of the dog Wave forms and timing data were gathered on a 5 mm array over the wall by multiple insertion of five differential electrode needles. Distance between electrodes on a needle is 1 mm

direction of the electrical activity is to be determined Knowledge that the activation front in the outer 4 mm of the left wall is propagating nearly in the direction of the electrodes is crucial to the statistical fitting of Equation 8 for the electric field because Equation 8 is determined by conditions which confine its applicability to the direction of motion for the wave front

Voltage measurements were made at 1 msec intervals The values were in millivolts from the baseline or quiescent level The wave forms were predominantly monophasic with both positive and negative maxima occurring Input polarity was chosen so that propagation from within outwardly resulted in positive maxima

Proagaption velocity was calculated from the time difference of voltage maxima at adjacent electrode pairs. Individual data channels were related to each other in time by means of the reference channel Velocity in meters per second was expressed as the distance between adjacent channels in millimeters divided by the difference in the times of voltage maxima

tatively alike. To reduce noise additional averaging was performed by combing the wave forms from each area thus the data examined consisted of 222 wave forms for the outer 4 mm. of the left ventricle.

Equation 8 was fitted to the data using 4 msec. on either side of the peak. A non linear least squares fit was used to find λ and E_o. Since there was a sizable number of data values at each millisecond the approximate 95 per cent confidence intervals were calculated at each point along the mean wave form using the method of multiple contrasts. Goodness-of-fit of the estimated function can be seen from these confidence intervals. The mean error-of estimate of the fitted function also was used to evaluate the fit. This evaluation involves comparing the mean error-of estimate over all data points to the measurement error variance. The ratio of these two quantities is a chi-square variable divided by its degrees-of-freedom. The ratio tests whether the error-of-estimate is comparable to the measurement error. The error variance in this experiment was estimated by computing the data variance at each millisecond and averaging across all time points. The confidence intervals and the chi-square test are two primary procedures for testing goodness-of-fit of a theoretical function to a set of data.

Discussion

The object of this study is to estimate the current dipole moment density associated with ventricular depolarization and use this estimate in a mathematical physical simulation of electrocardiographic data on the torso surface of humans. However the estimate obtained was for the dog and whether or not it represents a reasonable estimate for humans is still questionable. The results of Durrer and associates[14] confirm this uncertainty. They report bipolar complexes recorded in the human between successive terminals 2 mm. apart with voltages between 15 and 20 mv. They further report that the width of the excitatory wave is probably 1 to 1½ mm. These results yield an approximate value of $\Phi = 4 \times 10^{-12}$ m-coul per square meter which is lower than our estimate of 1.8×10^{-11} for the dog. Part of this difference can be attributed to the estimate of the electric field from their data which is probably low since intramural electrodes with a 2 mm separation will produce a mean value for E that is lower than that produced by electrodes with a smaller separation when measuring an excitatory wave with a width of the order of 1 to 1½ mm.

Another consideration in simplifying the simulation of myocardial activation is whether or not the current dipole moment density is constant throughout the myocardium. The experiments of Reynolds and Weller[13] conclude that there is a uniform difference in potential across all propagated wavefronts in the normal ventricular muscle of dog. If one assumes this uniformity in normal ventricular muscle of the human and combines it with the results of the Durrer group[14] which indicate less subendocardial Purkinje penetration in humans than dogs, then it seems reasonable to consider the current dipole moment density uniform throughout normal ventricular muscle.

Summary

A model of the current dipole moment associated with the region of the myocardium undergoing ventricular depolarization is postulated. The model was investigated in a series of dog experiments employing the technique of intramyocardial differential electrodes to measure the maximum electric field and distance between sources and sinks of current. Analysis yields a value of 26 mv. for the electromotive force of the activating front with a current dipole moment density of 1.8×10^{-11} coul-m per square meter. For the purpose of simulating electrocardiographic data in humans with a mathematical-physical model, the following first order approximation is given: the current dipole moment density associated with normal ventricular muscle undergoing depolarization is uniform throughout the myocardium with a value of 1.8×10^{-11} coul-m per square meter.

REFERENCES

1. Scher, A. M., and Young, A. C.: Ventricular depolarization and the genesis of QRS, Ann. N. Y. Acad. Sci. 65: 768, 1957.
2. Gelernter, H. L., and Swihart, J. C.: A mathematical-physical model of the genesis of the

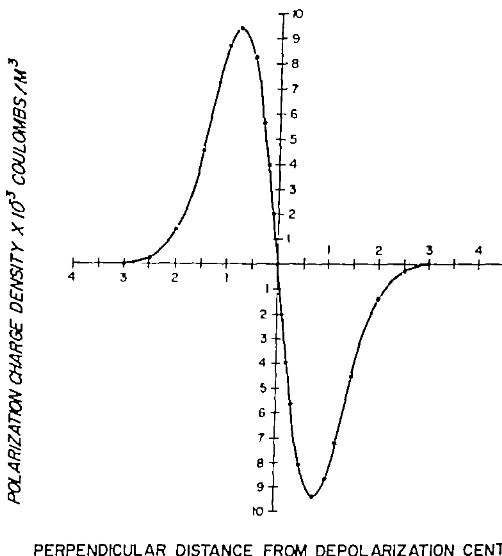


Fig 4 The polarization charge density equivalent to the current dipole density of the active region Distance between maximum and minimum represents the effective separation of the sources and sinks.

dipoles Fig 4 shows the form of Equation 10 The net separation of positive and negative charges is characteristic of a diffuse dipole layer the distance between the positive maximum and negative minimum is a measure of the thickness of the activating wavefront From the values estimated for E and λ the current dipole moment per unit area of this wavefront is approximately 1 8 × 10 $^{-12}$ m-coul per square meter

The electromotive force estimated from Equation 12 using the estimated values of E and λ yields a value of 26 mv for the outer 4 mm of the myocardium in the left ventricular wall of the dog This value is within the range of 20 to 30 mv reported in the experiments of Reynolds and Weller [15]

From the mathematical hypothesis a normal distribution was anticipated from differential electrode voltages. In the context of a mathematical model of the electrical activity in the heart it is the adequacy of this distribution which is of primary concern in this paper Due to the presence of a sizable amount of physiologic noise for individual wave data it was necessary to average a large number of waves to obtain an adequate estimate of the underlying form Averaging was accomplished by overlaying the maximum values of each wave form Since the waveform is initially and terminally zero it attains a maximum on its time interval and the mean waveform about the maximum is a representative member of the family of curves which are assumed to exist The mean wave forms from each outer 4 mm level of each area were quali

tatively alike. To reduce noise additional averaging was performed by combing the wave forms from each area thus the data examined consisted of 222 wave forms for the outer 4 mm of the left ventricle.

Equation 8 was fitted to the data using 4 msec. on either side of the peak. A non linear least squares fit was used to find λ and E_o. Since there was a sizable number of data values at each millisecond, the approximate 95 per cent confidence intervals were calculated at each point along the mean wave form using the method of multiple contrasts. Goodness-of fit of the estimated function can be seen from these confidence intervals. The mean error-of estimate of the fitted function also was used to evaluate the fit. This evaluation involves comparing the mean error-of estimate over all data points to the measurement error variance. The ratio of these two quantities is a chi-square variable divided by its degrees-of freedom. The ratio tests whether the error-of-estimate is comparable to the measurement error. The error variance in this experiment was estimated by computing the data variance at each millisecond and averaging across all time points. The confidence intervals and the chi-square test are two primary procedures for testing goodness-of fit of a theoretical function to a set of data.

Discussion

The object of this study is to estimate the current dipole moment density associated with ventricular depolarization and use this estimate in a mathematical physical simulation of electrocardiographic data on the torso surface of humans. However the estimate obtained was for the dog and whether or not it represents a reasonable estimate for humans is still questionable. The results of Durrer and associates[14] confirm this uncertainty. They report bipolar complexes recorded in the human between successive terminals 2 mm. apart with voltages between 15 and 20 mv. They further report that the width of the excitatory wave is probably 1 to 1½ mm. These results yield an approximate value of $\Phi = 10^{-12}$ m-coul per square meter which is lower than our estimate of 1.8×10^{-11} for the dog. Part of this difference can be attributed to the estimate of the electric field from their data which is probably low since intramural electrodes with a 2 mm separation will produce a mean value for E_o that is lower than that produced by electrodes with a smaller separation when measuring an excitatory wave with a width of the order of 1 to 1½ mm.

Another consideration in simplifying the simulation of myocardial activation is whether or not the current dipole moment density is constant throughout the myocardium. The experiments of Reynolds and Weller[15] conclude that there is a uniform difference in potential across all propagated wavefronts in the normal ventricular muscle of dog. If one assumes this uniformity in normal ventricular muscle of the human and combines it with the results of the Durrer group[14] which indicate less subendocardial Purkinje penetration in humans than dogs then it seems reasonable to consider the current dipole moment density uniform throughout normal ventricular muscle.

Summary

A model of the current dipole moment associated with the region of the myocardium undergoing ventricular depolarization is postulated. The model was investigated in a series of dog experiments employing the technique of intramyocardial differential electrodes to measure the maximum electric field and distance between sources and sinks of current. Analysis yields a value of 26 mv for the electromotive force of the activating front with a current dipole moment density of 1.8×10^{-11} coul m per square meter. For the purpose of simulating electrocardiographic data in humans with a mathematical-physical model the following first order approximation is given the current dipole moment density associated with normal ventricular muscle undergoing depolarization is uniform throughout the myocardium with a value of 1.8×10^{-11} coul m per square meter.

REFERENCES

1. Scher A. M. and Young A. C. Ventricular depolarization and the genesis of QRS, Ann. N. Y. Acad. Sci. 65:768, 1957.
2. Gelernter H. L., and Swihart J. C.: A mathematical-physical model of the genesis of the

electrocardiogram Biophys. J 4:285 1964
3 Selvester R H Solomon, J C and Gillespie T L. Mathematical model of the total body ECG with a reall tic external torso boundary Circulation 34:212 1966.
4 Scher A. M Young A C. Malmgren, A L., and Laton R. R. Spread of electrical activity through the wall of the ventricle Circ. Res. 1:539 1953
5 Scher A. M and Young A C. The pathway of ventricular depolarization in the dog Circ. Res. 4:161 1956
6 Durrer D Roos, J P and Buller J The spread of excitation in canine and human heart *in* Electrophysiology of the heart Pergamon Press 1964
7 Durrer D The human heart Some aspects of its excitation Tran and Studies of the College of Physicians of Philadelphia Ser 4 Vol 33 No 3 January 1966
8. Craib W H A study of the electrical field surrounding active heart muscle Heart 14:71 1927 1929
9 Durrer D and Van der Tweel L H Spread of activation in the left ventricular wall of the dog I AMER. HEART J 46:683 1953
10 Durrer D and Van der Tweel L. H: Spread of activation in the left ventricular wall of the dog II AMER. HEART J 47:192, 1953
11 Durrer D., Van der Tweel L. H and Blickman J R. Spread of activation in the left ventricular wall of the dog III AMER. HEART J 48:13 1954
12 Durrer D Van der Tweel L. H Berreklouw S and Van der Wey L. P Spread of activation in the left ventricular wall of the dog IV AMER. HEART J 50:850 1955
13 Selvester R. H Kirk W L. and Pearson R B: Propagation velocities and voltage magnitudes in local segments of myocardium Circ. Res. 27:1 1970
14 Durrer D Dam R Van T H. Meijler F L. Arzbaecher R. C. Muller E. J and Freud G E. Circulation (Suppl. 33 and 34) 11 92 1966
15 Reynold E. N Jr and Weller D A. An experimental study of the electromotive forces of the heart, AMER. HEART J 69:1 1965

Anatomic variations in the tetralogy of Fallot

B. N. Satyanarayana Rao, M.B.B.S.
Ray C. Anderson, M.D.
Jesse E. Edwards, M.D.
St. Paul, Minn.

In hearts bearing the complex of anomalies known as the tetralogy of Fallot the anatomic features fall within certain parameters. Yet within these, there are variations of a number of features such as (1) the basis for and the degree of pulmonary stenosis, (2) the course and branching of the aortic arch, (3) the state of the major pulmonary arteries and of the ductus arteriosus, and (4) association of other anomalies.

With these points in mind, an analysis was made of 85 specimens of heart exhibiting the characteristics of the tetralogy of Fallot. The report considers the various factors named and attempts to show whether or not relationships exist between these several factors.

Materials and methods

Eighty-five preserved specimens with the anatomic features of the tetralogy of Fallot from the Cardiovascular Registry of The Charles T. Miller Hospital and the Department of Pathology of The University of Minnesota were available for study. In the majority of cases, the aortic arch with its branches and the pulmonary arteries were present in the specimen, although in isolated cases one or another of the structures studied was either absent or in an inadequate state for interpretation.

In each case, the ventricular septal defect (VSD) was of the large variety situated posterior to a vertical crista supraventricularis. The aorta straddled the VSD, thereby arising from both ventricles. Continuity of the aortic and mitral valves was present in each case. Three specimens with persistent common atrioventricular canal, in addition to the anatomic characteristics of the tetralogy of Fallot, were included in this series.

Forty-one of the 85 specimens were from male patients and 41 from female patients. In 3 instances, the sex was unknown to us. The age at death ranged from two days to 43 years. The age was unknown in 6 cases, leaving 79 cases in which both the age and sex were known (Fig. 1). In 49 cases, operation had been done, 40 of the patients dying in the early postoperative period and 9 being examples of "late deaths."

The specimens were examined for a number of features including (1) the basis for pulmonary stenosis, (2) the nature of the

From the Department of Pathology, The Charles T. Miller Hospital, St. Paul, Minn., and the Departments of Pediatrics and Pathology, The University of Minnesota, Minneapolis, Minn.

This study was supported by Public Health Service Research Grant 5 R01 HE05694 and Research Training Grant 5 T01 HE05570 from the National Heart Institute and by the Dwan Family Fund.
Received for publication May 27, 1970.

Reprint requests to: Jesse E. Edwards, M.D., Department of Pathology, The Charles T. Miller Hospital, 125 West College Avenue, St. Paul, Minn. 55102.

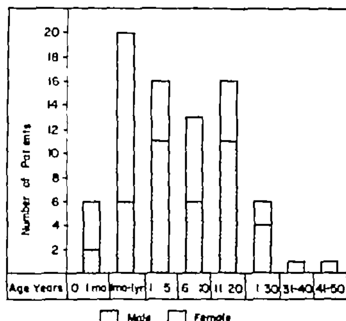


Fig 1 Age at death and sex of 79 patients with tetralogy of Fallot the specimens from which formed the basis of this study

pulmonary trunk and its branches (3) the nature of the aortic arch and its branches (4) the state of the ductus arteriosus, (5) the nature of the atrial septum (6) the presence of anomalies other than those which are part of the tetralogy complex and (7) the association of bacterial endocarditis Correlation was attempted between the presence of certain conditions and others.

Results

Pulmonary valve Obstruction to pulmonary flow may reside in the pulmonary valve the right ventricular infundibulum or the pulmonary trunk

In each specimen the pulmonary valve was inspected for the size of the annulus the nature of the valve the number of cusps the number and status of the commissures, and the caliber of the aperture Each pulmonary valve was classified as tricuspid (tricommissural) bicuspid (bicommissural) unicuspid (unicommissural) domed atretic, or absent.

The structure of the unicuspid valve was like that seen in certain cases of congenital aortic stenosis previously described by Edwards.[1] The term domed refers to a deformity of the pulmonary valve like that in pulmonary stenosis with intact ventricular septum

Table I indicates the distribution of degrees of pulmonary stenosis and the structure of the pulmonary valve In each of 21 specimens the pulmonary valve was atretic and represented by tissue of varying thickness interposed between the infundibulum and the pulmonary trunk From the ventricular aspect the pulmonary valve could not be visualized except as the base of a cul-de-sac at the distal end of the infundibulum In each case of pulmonary atresia the infundibulum was severely narrowed

Among the 59 specimens in which some opening was present at the pulmonary valve and in which the nature of the pulmonary valve could be determined the distribution of pulmonary valvular structure was as follows bicuspid 32 cases tricuspid 10 unicuspid 8 domed 7 and absent, 2

The caliber of the pulmonary valvular orifice was judged in comparison to that of the aortic orifice to develop designations of degrees of pulmonary valvular stenosis based upon comparison of diameters.

1 *Normal* The diameter of the pulmonary orifice was greater than 80 per cent of the aortic valvular diameter

2 *Mild to moderate stenosis* The pulmonary valvular orifice was between 50 and 80 per cent of aortic orifice.

3 *Severe stenosis* The pulmonary valvular orifice was less than 50 per cent of aortic.

4 *Pulmonary atresia* There was no communication between the infundibulum of the right ventricle and the pulmonary trunk

The individual cusps of bicuspid valve were usually short with corresponding limitation in mobility so that some degree of stenosis was thought to be present in 27 of the 32 bicuspid valves (84 per cent) Five of the 10 tricuspid valves were stenotic on the basis of a narrow orifice associated with short relatively rigid cusps while in the remainder the valve was not stenotic Each unicuspid and cone-shaped pulmonary valve exhibited stenosis of mild to-moderate or severe degree.

Considering the limited amount of material one could not observe a distinct trend for a type of pulmonary valve to be associated with a particular type of aortic arch Among the 21 cases of pulmonary atresia a right aortic arch was present in 9 cases

Table I Degree of stenosis and structure of pulmonary valve in 80 cases

Degree of pulmonary valvular stenosis	*Pulmonary valve structure*						
	Tricuspid	*Bicuspid*	*Unicuspid*	*Dome*	*Atresic*	*Absent*	*Total*
None	5	5	0	0	0	1	11
Mild–moderate	4	17	3	4	0	1	29
Severe	1	10	5	3	0	0	19
Pulmonary atresia	0	0	0	0	21	0	21
Total	10	32	8	7	21	2	80

Table II Pulmonary valvular and infundibular stenosis as observed in 84 cases

Infundibular stenosis	*Pulmonary valvular stenosis*				
	None	*Mild–moderate*	*Severe*	*Atresia*	*Total*
None	0	2	2	0	4
Mild–moderate	1	15	1	0	17
Severe	10	13	19	21	63
Total	11	30	22	21	84

(43 per cent) the overall incidence of right aortic arch being 29 per cent.

Right ventricular infundibulum. Table II shows the association of pulmonary valvular and infundibular stenosis in 84 specimens.

Infundibular stenosis was judged on the basis of the expected size of the infundibulum for the specimen in question, taking into account the narrowest portion of the infundibulum and the length of the hypoplastic segment or the number of sites of constriction when there were more than one. The difficulty of evaluating the degree of functional obstruction in fixed specimens is well recognized.

Among the 84 specimens in which the nature of the pulmonary valve and infundibulum was known, 32 had varying degrees of pulmonary valvular stenosis and 21 had pulmonary atresia. There were 4 cases with no infundibular stenosis and in each of these, the pulmonary valve was stenotic. Seventeen had mild-to-moderate infundibular stenosis and 63 showed severe infundibular stenosis, including the 21 cases of pulmonary atresia.

There was a strong tendency for the degree of infundibular obstruction to be concordant with the degree of valvular stenosis, although exceptions occurred as in 2 examples of severe valvular stenosis in which no infundibular stenosis occurred. In 10 cases, the reverse was true in that severe infundibular stenosis was associated with no valvular stenosis.

Pulmonary arteries. In 8 specimens, the pulmonary trunk was available and in 76 the 2 branches were present in the specimens. In one of the cases the nature of the pulmonary valve could not be determined.

The caliber of the pulmonary trunk was given certain designations by comparing its diameter to that of the aorta as follows:

1. *Normal.* The diameter of the pulmonary trunk was greater than 80 per cent of that of the aorta.

2. *Moderate hypoplasia.* The diameter of the pulmonary trunk was between 50 and 80 per cent of that of the aorta.

Table III. Pulmonary valvular stenosis and caliber of pulmonary trunk in 77 cases

Pulmonary trunk	Pulmonary valvular stenosis				
	None	Mild moderate	Severe	Atresia	Total
Normal	5	0	0	0	5
Moderate hypoplasia	4	5	5	7	41
Severe hypoplasia	0	0	12	11	23
Atretic	0	0	0	3	3
Poststenotic dilatation	1	4	0	0	5
Total	10	29	17	21	77

Table IV. Degree of infundibular stenosis and caliber of the pulmonary trunk as observed in 78 cases

Infundibular stenosis	Pulmonary trunk					
	Normal	Moderate hypoplasia	Severe hypoplasia	Atretic	Poststenotic dilatation	Total
None	0	1	2	0	1	4
Mild-moderate	0	14	1	0	1	16
Severe	6	26	20	3	3	58
Total	6	41	23	3	5	78

3. *Severe hypoplasia.* The diameter of the pulmonary trunk was less than 50 per cent of that of the aorta.

4. *Atresia.* There was no lumen in the pulmonary trunk which was represented by a fibrous-like strand of tissue.

5. *Poststenotic dilatation.* The relative size of the pulmonary trunk was disproportionately large compared to the orifice of the pulmonary valve.

Among 41 specimens with moderate hypoplasia of the pulmonary trunk only one showed a normal infundibulum and in this case there was a moderate degree of pulmonary valvular stenosis. Of the remaining 14 had moderate and 26 had severe infundibular obstruction.

Severe hypoplasia of the pulmonary trunk was strongly associated with major obstruction at the pulmonary valve and/or infundibulum.

There were 23 specimens with severe hypoplasia of the pulmonary trunk, including 2 with no infundibular stenosis but with moderate valvular stenosis and one with moderate infundibular and severe valvular stenosis. The remaining 20 showed severe infundibular stenosis, of which 1? manifested pulmonary atresia.

There were 3 specimens with atresia of the pulmonary trunk, each of which also exhibited atresia at the level of the pulmonary valve.

The basis for pulmonary stenosis varied among the 5 cases of poststenotic dilatation of the pulmonary trunk. In one only the pulmonary valve was stenotic. In a second case stenosis was present only in the infundibulum and in 3 cases both the valve and infundibulum were stenotic.

In comparing the pulmonary trunk with the pulmonary valve there was a strong tendency for the caliber of the vessel to decrease as the number of pulmonary cusps decreased and as the degree of pulmonary valvular stenosis increased (Table III).

Table V. Obstruction to pulmonary flow whether infundibular or valvular or both and the caliber of the pulmonary trunk as observed in 78 cases

Obstruction to pulmonary flow	Pulmonary trunk					
	Normal	Moderate hypoplasia	Severe hypoplasia	Atretic	Poststenotic dilatation	Total
Mild–moderate	1	14	0	0	2	17
Severe	5	20	12	0	3	40
Pulmonary atresia	0	7	11	3	0	21
Total	6	41	23	3	5	78

Table IV shows the relationship of the severity of the infundibular stenosis to the nature of the pulmonary trunk in 78 cases. Among the 4 specimens with no infundibular stenosis, the pulmonary trunk showed moderate hypoplasia in one, severe hypoplasia in 2 and poststenotic dilatation in one. Mild-to-moderate infundibular stenosis was present in 16 specimens, 14 of which showed moderate hypoplasia of the pulmonary trunk, one severe hypoplasia and one poststenotic dilatation of the pulmonary trunk.

The 58 specimens with severe infundibular stenosis included 6 with a normal pulmonary trunk, 26 with moderate hypoplasia 20 with severe hypoplasia, 3 with atresia of the pulmonary trunk, and 3 with poststenotic dilatation. Severe infundibular stenosis with only moderate pulmonary valvular stenosis had a strong tendency to be associated with only moderate hypoplasia of the pulmonary trunk. In contrast, when pulmonary valvular atresia was associated with severe infundibular stenosis, there was a wide range in the caliber of the pulmonary trunk. Among 21 specimens with pulmonary atresia and severe infundibular stenosis, 6 showed moderate hypoplasia, 12 severe hypoplasia, and in 3 atresia of the pulmonary trunk was present. In each of the 6 cases of a normal pulmonary trunk, there was severe infundibular stenosis without valvular stenosis.

If in our material, one combines valvular and infundibular stenosis as a basis for obstruction to pulmonary flow it becomes apparent that there is a direct relationship between the degree of restriction in caliber of the pulmonary trunk, on one hand, and the severity of pulmonary obstruction on the other (Table V). There is, however a greater tendency for valvular stenosis rather than infundibular stenosis alone to exert an effect on restriction in the caliber of the pulmonary trunk (Tables III and IV).

There was a strong tendency for the caliber of the right and left pulmonary arterial branches to be directly proportional to that of the pulmonary trunk, although in isolated instances the pulmonary trunk was severely hypoplastic while the branches showed lesser degrees of hypoplasia. In only 5 specimens was there a normal caliber of the pulmonary trunk and the 2 branches. Among 63 specimens with moderate or severe hypoplasia of the pulmonary trunk, the pulmonary artery branches were also hypoplastic. In 3 cases of moderate hypoplasia of the pulmonary trunk, there was localized stenosis of the branches, one bilateral and 2 unilateral.

One of the latter was an example of so-called "absence of the left pulmonary artery" ("proximal interruption of the left pulmonary arch" or "origin of the left pulmonary artery from the left ductus arteriosus"). The left pulmonary artery was stenotic at its ductal origin and showed slight poststenotic dilatation beyond the ductus, although the caliber beyond that level was very narrow compared to the expected normal. In each of the 3 specimens with an atretic pulmonary trunk the branches were patent but hypoplastic. In

Table VI Nature of aortic arch and degrees of obstruction to pulmonary flow whether infundibular or valvular as seen in 83 cases Percentages represent those of subgroups

Obstruction to pulmonary flow	*Right arch*	*Left arch*	*Total*
Mild–moderate	5 (26%)	14 (74%)	19 (100%)
Severe	10 (23%)	33 (77%)	43 (100%)
Atresia	9 (43%)	12 (57%)	21 (100%)
Total	24	59	83

Table VII Types of aortic arch and branches in 82 cases of the tetralogy of Fallot

Types of aortic arch and branches		*Number of specimens*
Major class	*Subclass*	
Double aortic arch	Both arches patent	1
	One arch patent	0
Left aortic arch	Normal branches	50
	Aberrant right subclavian artery	7
	Isolation of right subclavian artery	0
Right aortic arch	Mirror image branching	20
	Aberrant left subclavian artery	4
	Isolation of left subclavian artery	0
Total		82

the 5 cases of poststenotic dilatation of the pulmonary trunk the branches were essentially of normal caliber

There was no apparent relationship between the type of aortic arch and the character of the pulmonary trunk and its branches.

Aortic arch There were 84 cases in which both the basis for obstruction to pulmonary flow and the status of the aortic arch were known In 2 of these the nature of the branching of the aortic arch could not be determined In one of the 84 cases a double aortic arch was present.

Among the remaining 83 specimens, a right aortic arch was present in 24 cases (29 per cent) and a left aortic arch in 59 (71 per cent) (Table VI) In the 24 cases with a right aortic arch there were 10 cases of severe obstruction to pulmonary flow at the infundibulum the pulmonary valve or both in addition to 9 cases of pulmonary atresia Thus, 19 of 24 cases (77 per cent) with a right aortic arch manifested major obstruction to pulmonary flow

Among the 59 examples of left aortic arch major degrees of stenosis occurred in 45 cases (76 per cent)

In 82 of the cases the branches of the aortic arch were in an adequate state for interpretation (Table VII) The case of double aortic arch showed each arch to give rise to the common carotid and subclavian arteries of its side. In the 57 cases with a left arch the usual branching occurred in 50 while 7 cases showed an aberrant right subclavian artery (12 5 per cent of cases with left arch) Among the 24 cases of right aortic arch 20 showed a pattern of mirror image branching Four of the cases of right aortic arch showed an

Table VIII. Nature of the aortic arch and the status of the ductus arteriosus as observed in 80 cases, one of which was a case of double aortic arch with a ligamentum arteriosum present on the left side

Ductus arteriosus	*Aortic arch*		*Total*
	Right arch	*Left arch*	
Absent	7	12	19
Patent	4	15	19
Ligamentous	13	28	41
Total	4	55	79

Table IX. Status of ductus arteriosus and the degree of obstruction to pulmonary flow whether infundibular, valvular, or both, as observed in 81 cases

Status of ductus	*Degree of obstruction to pulmonary flow*			
	Mild-moderate	*Severe*	*Pulmonary atresia*	*Total*
Absent	2	12	5	19
Patent	2	5	12	19
Ligament	14	25	4	43
Total	18	42	21	81

anomalous left subclavian artery (16.5 per cent of cases with right arch). In each case of anomalous subclavian artery, whether right or left, the artery crossed from its aortic origin to the opposite side of the body behind the esophagus.

No cases of isolation of a subclavian artery[4] (origin of artery from a ductus arteriosus) were encountered in this study.

Ductus arteriosus. In each of 81 cases, the status of the ductus arteriosus could be determined and in each, except one, the nature of the aortic arch was known. Among 80 cases, the ductus arteriosus (or ligamentum arteriosum) was present on the left side in 60 cases (including the case with double aortic arch), on the right side in one case, and absent in 19 cases (Table VIII). No cases of bilateral ductus arteriosus were encountered. In the one case of a right ductus arteriosus, a right aortic arch was present. In those cases of a left ductus and a right arch, the ductus extended from the base of the left subclavian artery which arose from a left innominate artery and inserted into the left pulmonary artery. In each case of right arch with anomalous left subclavian artery, the ductus arteriosus was absent. In one of the cases of a patent left-sided ductus arteriosus, the ductus was continuous with the peripheral end of the left pulmonary artery, while the proximal segment of the left pulmonary artery was absent. The 19 cases of absence of the ductus were distributed as follows: seven cases among 24 cases of right aortic arch (29 per cent) and 12 cases among 55 cases of left aortic arch (22 per cent).

Patency of the ductus was encountered in 19 of the 61 cases with a ductus (30 per cent). The distribution of patent ductus according to the degree of obstruction to pulmonary flow was as follows (Table IX). In 16 cases of mild to-moderate obstruction to pulmonary flow and with a ductus present, the latter was patent in 2 cases. Comparable figures for severe pulmonary stenosis were 5 cases of patent ductus among

Table X. Degree of obstruction to pulmonary flow whether valvular infundibular or both and status of atrial septum as observed in 85 cases

Degree of obstruction to pulmonary flow	Atrial septum		
	Anatomically sealed	Valvular competent patent foramen ovale or ASD	Total
Mild–moderate	4 (21%)	15 (79%)	19
Severe	9 (20%)	36 (80%)	45
Pulmonary atresia	2 (9.5%)	19 (90.5%)	21
Total	15	70	85

In 4 cases, large defect in the lowermost part of the atrial septum was present. In 3, the defect was part of persistent A-V canal; in the fourth case the defect was associated with normal tricuspid and mitral valves (with pulmonary atresia).

30 cases. In pulmonary atresia the ductus was patent in 12 among 16 cases in which the ductus was present.

Atrial septum It was significant that a true or a potential interatrial communication was present in 70 of the 85 cases (82 5 per cent) In the majority (47 cases) this took the form of a valvular competent foramen ovale while in 23 cases there was a persistent opening between the 2 atria Usually this appeared to result from a short valve of the foramen ovale yielding a true through and through opening of less than one centimeter in diameter at the fossa ovalis. A large defect in the lowermost aspect of the atrial septum was present in 4 of the cases. In 3 of these the defect was part of the complex of persistent common atrioventricular canal while in one case the defect was associated with normal tricuspid and mitral valves

In spite of the fact that 35 per cent of the subjects in this study were infants below one year of age and 55 per cent were children under five years of age these figures suggest a strong tendency for the atrial septum to maintain some form of patency Some tendency for persistence of an interatrial communication seems to be related to the severity of obstruction to pulmonary flow (Table X)

While there was essential difference between cases having varying degrees of pulmonary stenosis, cases with pulmonary atresia exhibited a higher incidence of an interatrial communication than those with the various degrees of pulmonary stenosis.

Associated anomalies

Twenty nine specimens had associated anomalies in addition to the components of the tetralogy The following is a summary of observations in this regard

Left superior vena cava A left superior vena cava was present in 9 specimens (10 6 per cent) and drained into the coronary sinus in each

Persistent common atrioventricular canal In 3 specimens the features of the tetralogy were associated with the characteristics of the complete form of persistent common atrioventricular canal including its atrial septal defect and cleft condition of the atrioventricular valves. In one of these cases the mitral aspect of the common atrioventricular valve exhibited a parachute mitral valve like deformity in addition to an accessory orifice of the valve

Anomalies of the mitral valve. In addition to the cases with persistent common atrioventricular canal there were 3 instances of associated anomalies of the mitral valve One specimen showed localized hooding of the posterior leaflet associated with an accessory papillary muscle and accessory chordae In the second specimen a cleft was present in the anterior leaflet The third case showed cor triatriatum and anomalous chordae of the anterior leaflet of the mitral valve inserting into the ventricular septum the latter causing subaortic stenosis. This specimen was from a subject with omphalocele ectopia cordis, and a diaphragmatic hernia

Anomalies of the tricuspid valve There

were 3 instances of anomalies of the tricuspid valve exclusive of the 3 cases with persistent common atrioventricular canal A cleft in the septal leaflet of the tricuspid valve resulting in congenital tricuspid insufficiency was present in one specimen which also showed a systolic pocket of the left ventricle below the lower edge of the VSD The second specimen was from a patient with Down's syndrome in whom a cleft in the septal leaflet of the tricuspid valve and an atrial septal defect at the fossa ovalis were present. Bacterial endocarditis also involved the tricuspid valve in this case. In the third specimen with an anomalous tricuspid valve the valve showed an accessory pouch In addition an anomalous muscle bundle of the right ventricle and hypoplasia of the right coronary artery were present.

Miscellaneous conditions, each of which was encountered once in the entire series, were (1) Prolapse of the right aortic cusp with aortic insufficiency (2) subaortic stenosis (mentioned under anomalies of mitral valve) (3) accessory orifice of the mitral valve (in association with persistent A V canal) (4) aneurysm of the fossa ovalis (5) dextroversion (6) septal hypertrophy causing left ventricular outflow obstruction (7) left umbilical vein draining directly into the coronary sinus and absence of ductus venosus and (8) anomalous muscle bundle of the right ventricle causing subpulmonary stenosis (in a case with anomalous tricuspid valve)

Bacterial endocarditis

There were 5 specimens with evidence of bacterial endocarditis, the lesions being healed in the first 4 In 2 the infection appeared to have begun at the edges of a patch inserted to close the ventricular septal defect. The ages of the patients ranged from 15 to 39 years.

Comment

Though the tetralogy of Fallot has certain specific and well-recognized structural characteristics, a wide variation in the severity of the lesion and in association with other anomalies has been recognized

In this study those cases showing the cardiac structure of the tetralogy of Fallot were so classified whether or not pulmonary atresia was associated The relatively high incidence of cases with pulmonary atresia (21 of 85 cases) among our material may reflect a strong factor of selection The basis for this is that patients with pulmonary stenosis tend to live longer and to be more likely to receive the benefits of corrective surgery than do those with pulmonary atresia.

Among the cases of pulmonary stenosis it was the usual finding that stenosis at the infundibulum and pulmonary valve coexisted. It was relatively common nevertheless, as has been recognized that only the infundibulum would harbor the basis of obstruction to pulmonary flow (11 of 64 cases of pulmonary stenosis) In contrast stenosis only at the pulmonary valve was uncommon being present in only four of 64 cases of pulmonary stenosis. Some may disagree with the designation of the latter 4 cases as examples of the tetralogy The basis for including these examples in our study was that, in each the right ventricular infundibulum was a distinct tract, as in classical examples of tetralogy but without stenosis.

In each specimen with pulmonary atresia, there was hypoplasia of the entire right ventricular infundibulum the latter usually being represented by a small blind pouch anterior to the crista supraventricularis and terminating at the atretic pulmonary valve In other instances, there was a very narrow tortuous sinus-like tract leading to the atretic pulmonary valve

The structure of the pulmonary valve was studied in detail in our series. Adequate data regarding this subject are not available in reports of other series reviewed This study showed a strong tendency for the number of commissures in the valve to decrease as the severity of the pulmonary stenosis increased The degree of hypoplasia of the pulmonary trunk and pulmonary valvular abnormality in our series had a somewhat linear correlation Increasing degrees of hypoplasia of the pulmonary trunk were associated with a diminishing number of cusps and commissures in the valve. Also when the number of commissures in the pulmonary valve was decreased the pulmonary valvular annulus was proportionately hypoplastic. There was no definite correlation between the degree of

infundibular stenosis and hypoplasia of the pulmonary trunk

Hypoplasia of the pulmonary trunk was invariably associated with varying degrees of hypoplasia of the pulmonary arterial branches. There were however instances in which severe hypoplasia of the pulmonary trunk was associated with only mod erate hypoplasia of the pulmonary arterial branches. Even in the 3 specimens with atretic pulmonary trunk the branches of the pulmonary artery were represented by patent but severely hypoplastic pulmonary arterial branches There were 5 specimens with poststenotic dilatation of the pulmonary trunk 3 of which were associated with severe infundibular stenosis. In 3 of these specimens a bicuspid pulmonary valve was present and in each of 2 the pulmonary valve was absent

The high incidence of an interatrial com munication in tetralogy of Fallot has re ceived relatively little attention in the past It is of interest that only 15 of our cases (17 5 per cent) exhibited anatomic closure of the foramen ovale The high incidence of patency of the foramen ovale is probably the result of the right ventricu lar hypertrophy coupled with a low volume of blood in the left atrium

The incidence of right aortic arch in this series (29 per cent) is comparable to the incidence in some of the other series There has however been a wide discrepancy on the incidence of the right aortic arch among the several reported series[8,8] It was hy pothesized previously by one of the authors, Edwards that there was a correlation be tween the severity of the pulmonary outflow obstruction and the incidence of right aortic arch The analysis in this series however does not support this hypothesis There were 7 cases of anomalous right subclavian artery with left aortic arch and 4 cases of anomalous left subclavian artery with right aortic arch The incidence of anomalous subclavian artery is high compared to that in individuals without other malformations. In the general population an anomalous right subclavian artery occurs in about one in 200 persons.

Absence of the ductus arteriosus was fairly common in this series being observed in 19 of 79 cases (25 per cent) with a slightly greater tendency for right aortic arch to be associated with this condition than left. It is interesting to speculate on absence of the ductus as a response to low volumes of pulmonary flow in association with ready communication of the aorta with the right ventricle. The incidence of absent ductus was about equal in cases with pulmonary atresia as with pulmonary stenosis. The tendency for association with right aortic arch may perhaps result from peculiarities of streaming in right aortic arch contrasted with left arch

Of interest was the occurrence of bac terial endocarditis in 5 of the patients, in 2 of whom the infection began at the site of surgical closure of the ventricular septal defect The relatively older ages of the patients (age range 15 to 39 years) con forms with the tendency for bacterial endocarditis to involve older subjects more often than the young with congenital cardiac disease.

Intracardiac malformations associated with the tetralogy of Fallot although fairly numerous tended when present, to occur one per patient and probably reflects the phenomenon that the tetralogy has no particular affinity for association with a specific malformation except perhaps per sistent common atrioventricular canal The latter condition was seen in 3 of the 85 cases of the tetralogy the ages of the pa tients being 17 months, three years, and nine years In a fourth case involving a 2 year-old boy a defect in the lowermost part of the atrial septum was associated with normal mitral and tricuspid valves. Two of the patients with persistent com mon atrioventricular canal had Down s syndrome An additional case with the Down s syndrome had an intact atrial septum with a cleft in the tricuspid valve

The relatively common occurrence of persistent common atrioventricular canal and of Down s syndrome in our series may reflect a factor of selection as one of the contributors of specimens is an institution for the mentally deficient.

The relatively high incidence of patent ductus arteriosus may reflect the large proportion of infants in this series.

Summary

Eighty five specimens with a tetralogy of Fallot from patients varying in age from

infancy to adult life were studied for (1) the nature of the pulmonary valve the right ventricular infundibulum the pulmonary arteries, the aortic arch and the atrial septum and ( ) the association of other anomalies and of bacterial endocarditis.

The pulmonary valve was usually malformed only 10 of the cases exhibiting a tricuspid pulmonary valve. In the majority of instances (32 cases) a bicuspid valve was present. Pulmonary valvular atresia occurred in 21 cases. A unicuspid dome-shaped or absent pulmonary valve was seen in 8 7 and 2 cases, respectively Infundibular stenosis of some degree was present in all but 4 cases. Hypoplasia of the pulmonary trunk had a closer association with pulmonary valvular stenosis than with infundibular stenosis.

A right aortic arch was observed in 24 cases (29 per cent) The incidence of severe obstruction to pulmonary flow was about as common in cases of right aortic arch as in those with left arch Absence of the ductus arteriosus was observed in 19 cases. An interatrial communication was present in 70 cases (82.5 per cent) and usually took the form of a valvular competent foramen ovale.

Although associated intracardiac anomalies occurred in about 15 per cent of the cases, not all were functionally significant and there did not appear to be a tendency for the association of any one specific condition with the tetralogy Persistent common atrioventricular canal was seen in 3 cases. A persistent left superior vena cava occurred in 9 cases. Anomalous origin of the subclavian artery occurred more commonly than in the general population

Bacterial endocarditis was observed in 5 cases.

REFERENCES

1. Edwards, J E Pathologic aspects of cardiac valvular insufficiencies, Arch. Surg (Chicago) 77:634 1958.
2. Stewart, J R., Kincaid, O W and Edwards, J E. An atlas of vascular rings and related malformations of the aortic arch system, Springfield Ill. 1964 Charles C Thomas Publisher p. 171
3. Feigin, I and Rosenthal, J T tralogy of Fallot, Amer. Heart J 26:30. 1943
4. Baffes, T G., Johnson, F R., Potts, W J and Gibson, S. Anatomic variations in the tetralogy of Fallot, Amer. Heart J 46:657 1953
5. Brinton, W D and Campbell, M., Necropsies in some congenital diseases of the heart, mainly Fallot tetralogy Brit. Heart J 15 335, 1953
6. Rowe, R. D Vlad, P and Keith, J D Experiences with 180 cases of tetralogy of Fallot in infants and children, Canad. M A. J 73:23, 1955.
7. Lev M and Eckner F A. The pathologic anatomy of tetralogy of Fallot and its variations, Dis. Chest 45:251 1964,
8. Nagao, G. I Daoud G. I McAdams, A. J Schwartz, D C., and Kaplan, S.: Cardiovascular anomalies associated with tetralogy of Fallot, Amer J Cardiol. 20:206, 1967

Cardiovascular dynamics during coronary sinus, right atrial, and right ventricular pacing

Benjamin Befeler M D
Frank J Hildner M D
Roger P Javier M D
Lawrence S Cohen M D
Philip Samet M D
Miami Beach Fla

Traditional sites for permanent pacing of the human heart include the right and left ventricles and the right atrium In patients with normal atrioventricular conduction atrial pacing[1,2] is hemodynamically superior to ventricular pacing since it allows atrial contraction to precede ventricular systole and hence results in higher cardiac output Atrial pacing can be accomplished by the pervenous route or by direct implantation of epicardial wires at thoracotomy The chief disadvantage of epicardial electrode placement is the necessity for thoracotomy Atrial pacing could in theory be best accomplished by the pervenous route This technique has not proven reliable however since optimum catheter position is difficult to preserve[4] It has been suggested that the coronary sinus may serve as a stable site from which to pace the atrium[5] This could be useful in patients with sinus bradycardia sick sinus node syndrome with Stokes Adams attacks or congestive heart failure and in patients with recurrent supraventricular and ventricular paroxysmal arrhythmias[6-10] The purpose of the present study is to evaluate the hemodynamic consequences of this type of pacing as compared to right ventricular and right atrial pacing in patients with intact atrioventricular conduction

Material and methods

Fifteen patients ranging in age from 37 to 70 years mean age of 57 were studied in the postabsorptive state one hour after receiving 100 mg of Nembutal intramuscularly All subjects gave informed consent for the study Seven were women and 8 were men The diagnoses were coronary artery disease in 5 patients chronic bronchitis in 2 chest pain with normal coronary arteriograms in 2 and rheumatic heart disease with slight aortic insufficiency in 2 Sinus bradycardia rheumatic heart disease with mild aortic stenosis and rheumatic heart disease with minimal mitral insufficiency were present in three other subjects The last patient was found to be normal after study

A No 6 Goodale-Lubin catheter was

From the Division of Cardiology Department of Internal Medicine Mount Sinai Hospital, Miami Beach, Fla., and the Department of Medicine University of Miami School of Medicine, Coral Gables, Fla.
Received for publication June 18, 1970.
Reprint requests to Dr Befeler Mount Sinai Hospital, 4300 Alton Rd., Miami Beach, Fla. 33140.

March 1971 Vol 81 No 3 pp 372 380



Fig 1 Frame taken from a 35 mm cineangiogram during the injection of contrast medium the coronary sinus Note the dye flowing from the tip of the catheter back to the right atrium Simultaneous coronary sinus pacing is also shown In the left lower corner cine tracings of Lead 1 2 and 3 of the electrocardiogram and His bundle electrogram recorded by another bipolar electrode catheter placed at the tricuspid valve. A third catheter is in the pulmonary artery for injection of Cardio-Green for measurement of cardiac output.

introduced into the right heart chambers, in the usual manner under fluoroscopic control via a venous cutdown from the right or left arm Pressures were recorded from the right atrium right ventricle pulmonary artery and pulmonary capillary wedge positions. The left brachial or left femoral artery was cannulated with a Cournand needle using standard techniques. Cardiac output was estimated in duplicate by the indicator dilution technique injecting indocyanine green in the pulmonary artery and sampling from the left radial or left femoral artery A No 5 catheter with a bipolar electrode and a lumen was introduced through the same vein or another basilic vein and advanced to the right atrium and manipulated into the coronary sinus and advanced into the great cardiac vein to a position which appeared to the left of the spine on fluoroscopy The location of the catheter within the coronary sinus was confirmed by sampling blood which showed a low oxygen saturation by injection of contrast medium into the sinus and demonstration of its typical anatomic appearance (Fig 1) or by demonstration of two equal-sized spikes on a bipolar electrogram which represent atrial and ventricular depolarization (Fig 2) as shown previously by others Atrioventricular conduction was studied during atrial pacing starting approximately 10 beats above resting rates and progressively increasing the pacing rate up to a level where either Wenckebach cycles or 2 1 atrioventricular (A V) block would develop Once normal A V conduction was established in a given patient the hemodynamic study was initiated. Baseline measurements included cardiac output and systemic and pulmonary artery pressures Coronary sinus pacing was then commenced at a rate of about 15 beats per minute above resting and maintained for a minimum of two minutes to reach a steady state as demonstrated in a previous study [11] This was called first level of coronary sinus pacing the above measurements were repeated after which the pacing rate was increased approximately another 15 beats per minute this was called second level of coronary sinus pacing The procedure was repeated for right ventricular and right atrial pacing at two similar

Cardiovascular dynamics during coronary sinus, right atrial, and right ventricular pacing

Benjamin Befeler M D
Frank J Hildner M.D
Roger P Javier M D
Lawrence S Cohen M.D
Philip Samet M D
Miami Beach Fla

Traditional sites for permanent pacing of the human heart include the right and left ventricles and the right atrium In patients with normal atrioventricular conduction atrial pacing[1,2] is hemodynamically superior to ventricular pacing since it allows atrial contraction to precede ventricular systole and hence results in higher cardiac output Atrial pacing can be accomplished by the pervenous route or by direct implantation of epicardial wires at thoracotomy The chief disadvantage of epicardial electrode placement is the necessity for thoracotomy Atrial pacing could in theory be best accomplished by the pervenous route This technique has not proven reliable however since optimum catheter position is difficult to preserve[4] It has been suggested that the coronary sinus may serve as a stable site from which to pace the atrium[5] This could be useful in patients with sinus bradycardia sick sinus node syndrome with Stokes Adams attacks or congestive heart failure and in patients with recurrent supraventricular and ventricular paroxysmal arrhythmias[6-10] The purpose of the present study is to evaluate the hemodynamic consequences of this type of pacing as compared to right ventricular and right atrial pacing in patients with intact atrioventricular conduction

Material and methods

Fifteen patients ranging in age from 37 to 70 years mean age of 57 were studied in the postabsorptive state one hour after receiving 100 mg of Nembutal intramuscularly All subjects gave informed consent for the study Seven were women and 8 were men The diagnoses were coronary artery disease in 5 patients chronic bronchitis in 2 chest pain with normal coronary arteriograms in 2 and rheumatic heart disease with slight aortic insufficiency in 2 Sinus bradycardia rheumatic heart disease with mild aortic stenosis and rheumatic heart disease with minimal mitral insufficiency were present in three other subjects. The last patient was found to be normal after study

A No 6 Goodale-Lubin catheter was

From the Division of Cardiology Department of Internal Medicine Mount Sinai Hospital, Miami Beach, Fla and the Department of Medicine University of Miami School of Medicine Coral Gables, Fla.
Received for publication June 18, 1970.
Reprint requests to Dr Befeler Mount Sinai Hospital, 4300 Alton Rd., Miami Beach, Fla. 33140.

Table I. Summary of mean values for cardiac index, mean systemic pressure, and mean pulmonary artery pressure

Level	Parameters					P value
	Cardiac index (L./min./M.²)					
	CSP		vs.	RAP		
1st	2.38	0.41†		2.37	0.40†	>0.25‡
2nd	2.45	0.42		2.41	0.37	>0.25‡
	RAP		vs.	RVP		
1st	2.37	0.40		1.87	0.36	<0.005
2nd	2.42	0.37		1.88	0.41	<0.005
	CSP		vs.	RVP		
1st	2.38	0.41		1.87	0.36	<0.005
2nd	2.45	0.42		1.88	0.41	<0.005
	Mean systemic pressure (mm. Hg)					
	CSP		vs.	RAP		
1st	103	7		101	9	>0.20*
2nd	106	9		103	10	>0.20‡
	RAP		vs.	RVP		
1st	101	9		92	15	<0.05
2nd	103	10		95	16	>0.10‡
	CSP		vs.	RVP		
1st	103	7		92	15	<0.05
2nd	10[illegible]	9		95	16	<0.05
	Mean pulmonary artery pressure (mm. Hg)					
	CSP		vs.	RAP		
1st	13	5		13	4	>0.15
2nd	14	4		13	4	>0.20‡
	RAP		vs.	RVP		
1st	13	4		17	4	<0.05
2nd	13	4		18	4	<0.005
	CSP		vs.	RVP		
1st	13	5		17	4	>0.15‡
2nd	14	4		18	4	<0.05

Abbreviations: CSP, Coronary sinus pacing; RVP, right ventricular pacing; RAP, right atrial pacing.
*In this vertical column, all values are mean values.
†In this vertical column, all values are standard deviation values.
‡Differences are not statistically significant.

sinus pacing mean cardiac index was 2.38 L. per minute per square meter (min./M.²) during right atrial pacing the mean index was 2.37 ($p > 0.25$). The second level coronary sinus pacing index was 2.45 L./min./M.² and that from the right atrial pacing was 2.41 ($p > 0.25$). Ventricular pacing, as shown previously,[1-4] resulted in a lower cardiac index at the first level, 1.87 L./min./M.², 21.5 per cent lower than coronary sinus pacing ($p < 0.005$) and 21.4 per cent lower than right atrial pacing ($p < 0.005$). For the second level of right ventricular pacing the mean cardiac index was 1.88 L./min./M.², 23.3 per cent lower than coronary sinus pacing ($p < 0.005$) and .3 per cent lower than right atrial pacing ($p < 0.005$) (Figs. 6 and 7).

Mean systemic pressures were similar for right atrial and coronary sinus pacing. During right ventricular pacing, as compared with *right* atrial pacing, mean systemic pressure was significantly lower for the first level ($p < 0.05$) and also

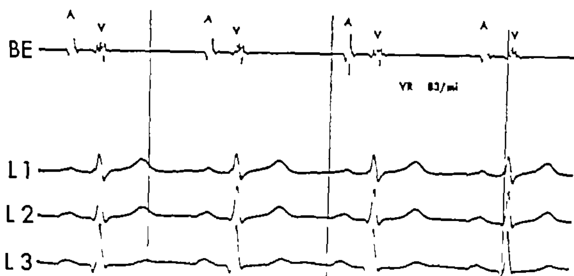


Fig 2 A bipolar electrogram is recorded within the coronary sinus showing atrial (A) and ventricular (V) potentials. Electrocardiographic leads are 1 2 and 3

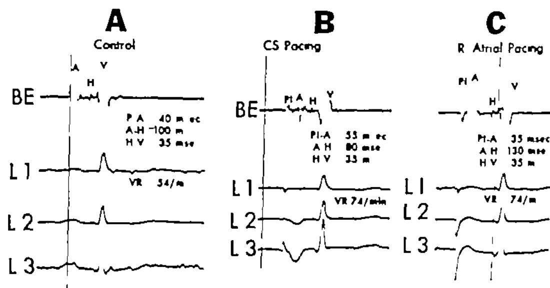


Fig 3 A His bundle recording with Leads 1 2 and 3 of the ECG at rest. B His bundle electrogram during coronary sinus pacing A H 80 msec. H V 35 msec. C Same recording as "B" during right atrial pacing Note that QRS complex is narrow during coronary sinus pacing and right atrial pacing and H V time is normal.

rates and the same measurements made. The data obtained were subjected to statistical analysis utilizing the Student t test [13]

Results

All 15 patients showed normal atrioventricular conduction as demonstrated by a normal P R interval in the conventional electrocardiogram and exhibited 1 1 conduction with atrial pacing up to 140 to 150 beats per minute.[14]

The appearance of the surface electrocardiogram during coronary sinus pacing as compared to normal sinus rhythm and right atrial pacing is shown in Fig 3 As reported by others[15] the rhythm appeared like the so-called left atrial rhythm with P waves preceding a narrow QRS complex negative in Leads II III aV_F and V_6 (Fig 4)

Hemodynamic studies (Table I) demonstrate that the atrial contribution to stroke volume is present during coronary sinus rhythm as shown by the almost identical values for cardiac index at two levels of pacing from the coronary sinus and the right atrium (Fig 5) First level coronary

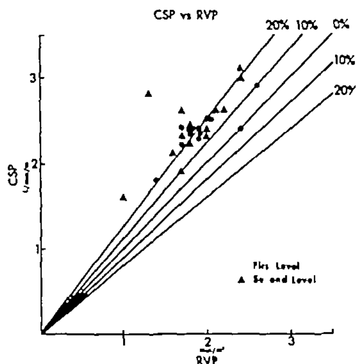


Fig. 6 Cardiac index during coronary sinus pacing and right ventricular pacing. Most outputs are higher during coronary sinus pacing than during right ventricular pacing

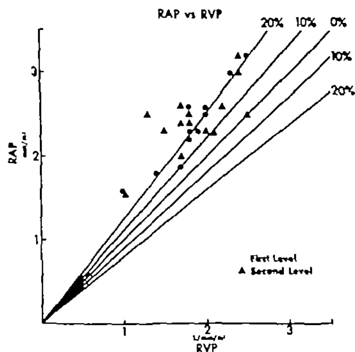


Fig 7 Cardiac index during right atrial pacing and right ventricular pacing. Cardiac index falls during right ventricular pacing.

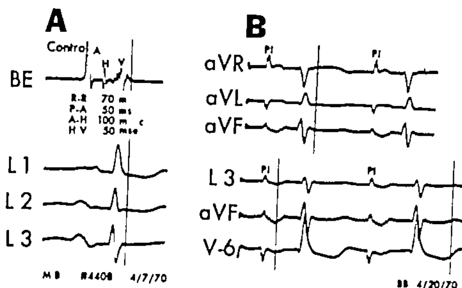


Fig 4 A His bundle electrogram with Lead 1 2 and 3 B Leads aV$_R$ aV$_F$ aV$_L$ L$_3$ and V during coronary sinus pacing Note narrow QRS complexes and inverted P waves in Leads 3 aV$_F$ and V$_6$. P waves are upright in Leads V$_R$ and aV$_L$

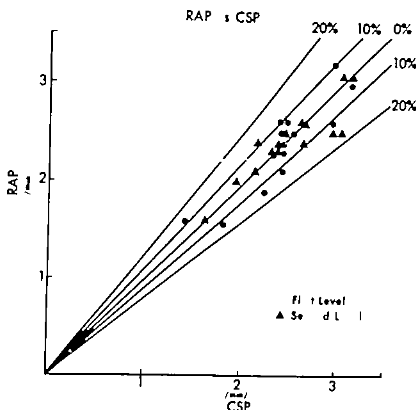


Fig 5 Comparative graph of cardiac index during coronary sinus pacing (abscissa) and right trial pacing (ordinate) The zero line is the line of identity

lower for the second level but these differences were not statistically significant ($p > 0.10$) When mean systolic pressure during ventricular pacing is compared to that during coronary sinus pacing the mean systolic pressure during ventricular pacing is lower at both levels of pacing ($p < 0.05$ for both)

Mean pulmonary artery pressure was slightly different during coronary sinus and right atrial pacing (first level $p > 0.15$ second level $p > 0.20$) but these differ

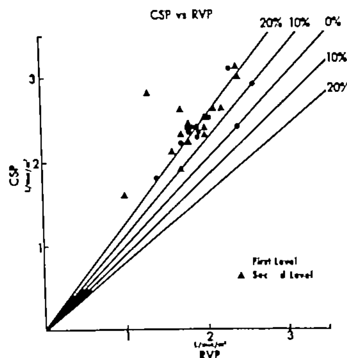


Fig. 6 Cardiac index during coronary sinus pacing and right ventricular pacing. Most outputs are higher during coronary sinus pacing tha during right ventricular pacing.

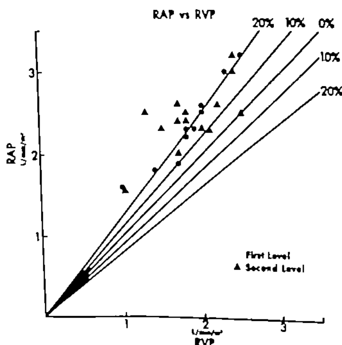


Fig 7 Cardiac index during right trial pacing and right ventricular pacing Cardiac index falls during right ventricular pacing.

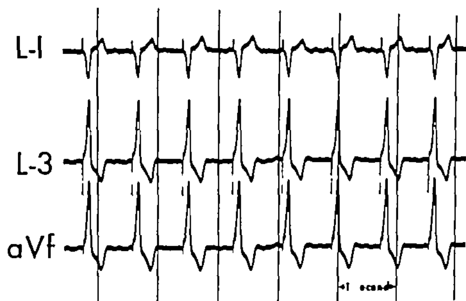


Fig 8 Leads 1 2 and 3 during coronary sinus pacing with the pacer electrode as far distal as possible in the coronary sinus resulting in a left ventricular pacing pattern with a right bundle branch block configuration.

ences are not statistically significant. During ventricular pacing mean pulmonary artery pressure was higher and the difference is significant when compared with right atrial pacing at the first level ($p < 0.05$) and at the second level ($p < 0.005$) At the first level of ventricular pacing when compared with coronary sinus pacing the mean pulmonary artery pressure was higher but the difference was not statistically significant ($p < 0.15$) at the second level the mean pulmonary artery pressure was also higher and significantly different statistically ($p < 0.05$)

Pacing threshold as defined by the milliamperage capable of capturing the heart, was always found to be less than 1 Ma. in the coronary sinus and pacing from this site appeared stable during the 15 minutes of the study Wide QRS complexes with a right bundle branch block pattern could sometimes be produced when the pacing catheter was placed deep in the coronary sinus evoking a left ventricular pacing rhythm as shown previously[11] (Fig 8)

Discussion

Atrial pacing is indicated in a number of conditions in which the atrioventricular conduction is intact. Permanent pervenous atrial pacing has not been reliable in the past. Pacing from the coronary sinus might be an ideal site if proven to be hemodynamically similar to atrial pacing Lancaster and associates[17] demonstrated that coronary sinus pacing induces a rhythm characterized by a P R interval greater than 0 12 second with a P wave occurring before a normal (narrow) QRS complex the P wave being inverted in Leads II III and aV_F The same authors showed that the P wave vector was directed superiorly anteriorly and slightly to the right. The duration of the P R segment in a group of 8 patients during coronary sinus pacing was between 0 13 and 0 24 second Based on these observations they suggested that atrial excitation is retrograde during coronary sinus pacing and that coronary sinus rhythm is synonymous with the so-called upper nodal rhythm The present study suggests that the sequence of activation of the atria and the ventricles occurs in the usual antegrade manner as demonstrated by the presence of an atrial potential preceding the His bundle deflection during coronary sinus as well as during right atrial pacing (Fig 3)

Recent developments in permanent pervenous atrial pacing include the design of a special J-shaped catheter placed in the right atrial appendage[4,19] The latter experience is relatively small and as with other previously used atrial catheters problems such as loss of capture pacing

the diaphragm and high threshold can occur

The present studies show that cardiac index, systemic pressure, and pulmonary artery pressure are very similar during right atrial pacing and coronary sinus pacing. Therefore, coronary sinus pacing could in theory be utilized in individuals with intact atrioventricular conduction as a site for permanent pacing of the heart. A recent report of a small number of cases[8] suggests that no ill effects result from leaving a catheter in the coronary sinus, although the theoretical possibility of coronary sinus thrombosis exists, and long term follow-up of patients treated with this type of pacing should be carried out. Permanent pervenous atrial pacing in the past had not proven reliable when the catheter was positioned in the right atrial appendage such catheters have been shown to have higher pacing thresholds.[4] This has not been the case in this study of acute coronary sinus pacing the threshold in every one of our cases has been below 1 Ma.

Summary

Permanent pervenous right atrial pacing has not been widely used to date. The coronary sinus may provide a site from where reliable permanent pacing can be performed so as to preserve atrial contribution in patients with intact A V conduction who require pacing as in sinus bradycardia, sinus arrest and recurrent tachyarrhythmias.

To test this hypothesis, 15 individuals, 37 to 70 years old (average 56 6 years) with a variety of heart diseases but with normal A V conduction were studied. After control cardiac index had been obtained coronary sinus, right atrial pacing and right ventricular pacing were performed at two levels above the control sinus rate. Mean cardiac index was virtually identical for coronary sinus and right atrial pacing at the first level, 2.38 and 2.37 L./min./M respectively and at the second level 2.45 and 2.42 L./min./M respectively. During the first level of right ventricular pacing mean cardiac index was 1.87 L./min./M 21.8 per cent lower than during coronary sinus pacing ($p < 0.005$) and 21.4 per cent lower than right atrial pacing ($p < 0.005$). For the second level of right ventricular pacing the mean cardiac index was 1.88 L./min./M[2] 23.3 per cent lower than during coronary sinus pacing ($p < 0.005$) and 22.3 per cent lower than right atrial pacing ($p < 0.005$). Systemic pressures were similar during right atrial and coronary sinus pacing and lower during right ventricular pacing at both pacing levels. Pulmonary artery pressure was higher during right ventricular pacing at both levels.

The coronary sinus provides an area from which the heart can be paced with the hemodynamic advantages of atrial pacing if intact A V conduction exists.

The authors wish to thank Duane Postlethwait for preparing the illustrations. We wish to thank William R. Oliver Abraham Embi, and the technologists of the Cardiovascular Laboratory for their invaluable assistance. W are indebted t Lee Ann Moffett, Mary Ann Westbury and Helen Comaso for typing the manuscript.

REFERENCES

1. Samet, P Castillo, C., and Bernstein, W H. Hemodynamic consequences of atrial and ventricular pacing in subjects ith normal hearts, Amer J Cardiol. 18:522, 1966.
2. Samet, P Castillo, C., and Bernstein, W H: Hemodynamic sequelae of atrial, ventricular and sequential atrioventricular pacing in cardiac patients, Amer. Heart J 72 725 1966.
3. Samet, P Bernstein, W H., and Levine, S. Significance of the atrial contribution to ventricular filling Amer J Cardiol. 15 195 1965.
4. Kastor J Q DeSanctis, R. W Leinbach, R. C., Harthorne, J W and Wolfson, W N Long term pervenous trial pacing Circulation 40:535 1969
5. Gonzalez, L. L. Discussion, Arch. Surg 97:990 1968.
6. Kastor J A., DeSanctis, R. W Harthorne, J W and Schwartz, G. A.: Transvenous atrial pacing in the treatment of refractory ventricular irritability Ann. I tern. Med. 66:939 1967
7. DeFrancis, N A., and Giordano, R. P., Permanent epicardial trial pacing in the treatment of refractory ventricular tachycardia, Amer J Cardiol. 22 742, 1968.
8. Moss, A. J Rivers, R. J Griffith, L. S C., Carmel, J A., and Millard, E. B., J Transvenous left trial pacing for control of recurrent ventricular fibrillation, New Eng J Med. 278:928, 1968.
9. Hornbaker J H., J Humphries, J O and Ross, R. S. Permanent pacing in the absence of heart block, Circulation 39:189 1969
10. Zipes, D P Festoff, B., Schaal, S. F., Cox, C., Sealy W C., and Wallace, A. G.: Treatment of ventricular arrhythmia by permanent

atrial pacemaker and cardiac sympathectomy Ann. Intern. Med 68:531 1968
11 Levine, H D and Goodale W T Studies in intracardiac electrography in man. IV The potential variations in the coronary venous system Circulation 2:48 1950
12 Samet P Bernstein W H Levine, S and Lopez A. Hemodynamic effects of tachycardias produced by atrial and ventricular pacing Amer J Med 39:905 1965
13 Student Probable error of mean Biometrika 6:1 1908
14 Lister J W Stein E. Kosowsky B D Lau S H and Damato, A. N Atrioventricular conduction in man. Effect of rate exercise isoproterenol and atropine on the P R interval Amer J Cardiol. 16:516 1965
15 Moss, A J Rivers, R. J and Cooper M Long term pervenous atrial pacing from the proximal portion of the coronary vein, J.A.M.A. 209:543 1969
16 Barold S S. Narula O S Javier R. P Linhart J W., Lister J W., and Samet, P Significance of right bundle branch block patterns during pervenous ventricular pacing Brit. Heart J 31:285 1969
17 Lancaster J F Leonard J J Leon D F Kroetz, F W and Shaver J A. The experimental production of coronary sinus rhythm in man AMER. HEART J 70:89 1965
18 Smyth N P D Vasarhelyi, L. McNamara W., and Kakasdi. G E. A permanent transvenous atrial electrode catheter J Thorac. Cardiovasc. Surg 58:773 1969

Experimental evaluation of pentazocine
Effect on myocardial contractility and peripheral vascular resistance

Sidney Levitsky M.D
Edward M Mullin M.D
Robert E. Sloane M.D
Andrew G Morrow M.D
Bethesda Md

In an attempt to synthesize a nonaddicting analgesic agent, pentazocine derived from the benzomorphan nucleus, was developed as an effective but nonaddicting analgesic agent. Administration of this drug especially to patients with low blood pressure following myocardial infarction has resulted in frequent but unexplained rises in systolic blood pressure. These observations suggested that the drug might have a positive inotropic effect but the effect on blood pressure could also or instead result from an effect on peripheral vascular resistance. Since pentazocine is often administered to patients who have had cardiac operations or myocardial infarction a detailed study of the effects of this drug on myocardial contractility and peripheral vascular resistance appeared indicated.

Methods

Thirty-two mongrel dogs weighing 16.4 ± 4.9 kg were used. Anesthesia was induced with sodium pentobarbital (30 mg per kilogram). A right heart bypass preparation that permitted the regulation of coronary and systemic arterial perfusion pressures was used (Fig 1). A large cannula placed into the right atrium and right ventricle diverted all blood returning to the heart into a graduated cylinder and subsequently returned the effluent to the pump oxygenator.

After extracorporeal circulation was initiated the main pulmonary artery was ligated and the left atrium opened widely. The mitral valve leaflets and chordae tendineae were excised. A soft latex balloon mounted on a Teflon perforated plug was inserted into the left ventricle and held in place by a purse-string suture encompassing the mitral annulus. A small disc mounted as a side-arm on the mitral plug prevented the inflated balloon from herniating through the aortic valve during ventricular contraction. A 3 mm metal cannula in direct continuity with the balloon emerged from the plug and was connected by suitable rigid couplings to two pressure transducers (Statham p23h) for

From the Clinic of Surgery, National Heart and Lung Institute, Bethesda, Md.
Received for publication June 18, 1970.
Reprint requests to: Dr. Andrew G. Morrow, Chief, Clinic of Surgery, National Heart and Lung Institute, Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, Md. 20014.
*Talwin, Winthrop Labs., New York, N. Y.

atrial pacemaker and cardiac sympathectomy Ann. Intern. Med 68:531 1968.
11 Levine, H D and Goodale, W T Studies in intracardiac electrography in man. IV The potential variations in the coronary venous system Circulation 2:48 1950
12. Samet P Bernstein, W H Levine S and Lopez, A.: Hemodynamic effects of tachycardias produced by atrial and ventricular pacing Amer J Med. 39:905 1965
13 Student Probable error of mean Biometrika 6:1 1908.
14. Lister J W Stein, E. Kosowsky B D Lau S. H., and Damato A. N Atrioventricular conduction in man Effect of rate exercise isoproterenol and atropine on the P R interval Amer J Cardiol. 16:516 1965
15 Moss, A. J Rivera, R. J and Cooper M Long term pervenous atrial pacing from the proximal portion of the coronary vein J.A.M.A 209:543 1969
16. Barold S S Narula O S. Javier R. P., Linhart J W Lister J W and Samet P: Significance of right bundle branch block patterns during pervenous ventricular pacing Brit. Heart J 31:285 1969
17 Lancaster J F., Leonard J J., Leon D F Kroetz F W and Shaver J A. The experimental production of coronary sinus rhythm in man Amer Heart J 0:89 1965
18 Smyth N P D Vasarhelyi L., McNamara W and Kakascik, G E. A permanent transvenous atrial electrode catheter J Thorac Cardiovasc. Surg 58:773 1969

weight of the left ventricle including the interventricular septum was determined after the right ventricle and both atria had been excised.

Coronary blood flow was measured by the timed collection of the right heart drainage. The oxygen content of coronary arterial blood and of blood drained from the right heart was measured manometrically and used to calculate myocardial oxygen (MVO). In 6 animals beta adrenergic blockade was induced with propranolol (0.15 to 0.25 mg per kilogram) after an isoproterenol dose-response curve had been performed. After verification of the presence of beta blockade by readministration of the highest dose of isoproterenol, pentazocine was infused into the dog and high speed tracings obtained.

Six animals were depleted of catecholamines by the administration of reserpine, 0.5 mg per kilogram daily in divided doses over a 48 hour period. Normal saline solution in a dose equivalent to 8 to 10 per cent of body weight was given intravenously each day to compensate for the severe diarrhea and vomiting often noted in these animals. After a stable basal state was achieved on right heart bypass, tyramine (20 μg per kilogram) was administered to verify catecholamine depletion. Pentazocine was then administered and high speed tracings obtained.

In 2 intact dogs, a flow transducer (Biotronex 610) was placed around the ascending aorta 24 hours before the study. At the time of the study an end-hole catheter was introduced into the LV under fluoroscopic control. A second catheter inserted into the aorta measured systemic arterial pressure. Observations were made during a control period and following the intravenous administration of 1.5 mg per kilogram pentazocine.

Statistical analysis was performed on a CEIR basic computer programmed to compare grouped data with unequal variance. Individual groups were compared using a one tailed Student t test.

Results

Ventricular contractility. In 20 dogs given only pentazocine, the LVP increased by 28 per cent, rising from 85.0 ± 7.0 mm Hg to 109.2 ± 8.5 mm Hg ($p < 0.001$). The peak effect was sustained up to 40 minutes after injection. Similarly, LV dp/dt max. rose 46 per cent, from $1{,}720 \pm 164$ to $2{,}540 \pm 229$ mm. Hg per second ($p < 0.001$). LVEDP remained essentially unchanged, 6.8 ± 0.7 before and 6.4 ± 0.7 mm. Hg after the drug was administered (Table I). The force-velocity curve was shifted upward and to the right, indicating an increase in contractility (Fig. 2). Coronary blood flow and myocardial oxygen consumption were unaltered by the administration of pentazocine.

In the animals pretreated with propranolol, the LVP rose slightly from 40.1 ± 11.2 to 42.9 ± 11.7 mm. Hg, and LV dp/dt max. similarly increased only 12 per cent from $1{,}022 \pm 323$ to $1{,}154 \pm 378$ mm Hg per second ($p < 0.10$). No significant change was seen in LVEDP. In the reserpinized animals, the LVP increased 21 per cent from 49.8 ± 27.3 to 60.5 ± 33.7 mm. Hg ($p < 0.05$) and the LV dp/dt max. increased 38 per cent from 479 ± 260 to 661 ± 330 mm. Hg per second ($p < 0.01$). The LVEDP was unaltered (Table I).

Response time—peripheral vascular resistance. All animals not given propranolol or reserpine exhibited a fall in peripheral vascular resistance from 57.7 ± 18.0 to 24.5 ± 13.8 resistance units (42.5 per cent) within 2 minutes after the intravenous administration of pentazocine ($p < 0.001$). Invariably the peripheral resistance returned to a normal level within three minutes. Changes in LVP and LV dp/dt max. were first noted 5 to 10 minutes after injection and were sustained for the entire period of study.

Intact animals. In the 2 closed-chest animals previously prepared, the LVP rose 22 per cent, the LV dp/dt max. 61 per cent, and the flow velocity 51.9 per cent, 10 to 15 minutes after the intravenous injection of pentazocine.

Discussion

Other investigators have shown in patients who have had myocardial infarction, that pentazocine usually causes a transient fall in blood pressure followed by a rise. A consistent rise in blood pressure has also been noted when pentazocine is used alone

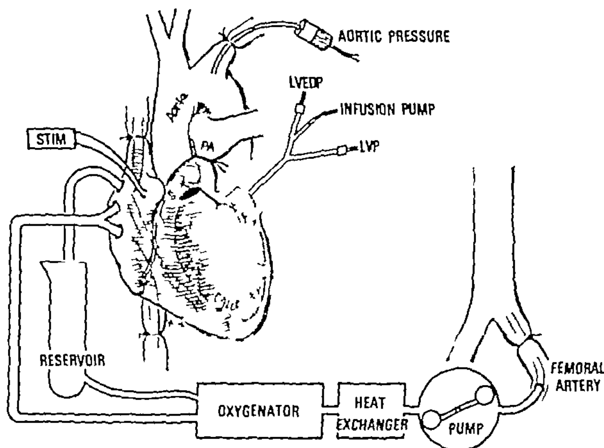


Fig 1 Right heart bypass preparation utilized to obtain left ventricular (*LV*) force-velocity curves. Heart rate was maintained constant for each experiment by electrical stimulation of the right atrium LV balloon volume was fixed by infusion of a known amount of saline Throughout each study the aortic pressure was *maintained at 75 mm. Hg* by continuous adjustment of the arterial inflow pump.

simultaneous measurement of left ventricular pressure (LVP) and left ventricular end-diastolic pressure (LVEDP) In addition a stiff vinyl catheter connected to a calibrated syringe was used to vary balloon volume (Fig 1) Another cannula was placed in the thoracic aorta for registration of aortic pressure The sinoatrial node was crushed and a constant heart rate of 120 to 150 beats per minute was maintained by electrical stimulation of the right atrium Body temperature was monitored and maintained between 36 5° and 37 5° C The analog signals were fed into a Sanborn 350 direct writing recorder The first derivative of the left ventricular pressure signal (LV dp/dt max) was obtained with an analog differentiating circuit

After the mitral valve plug was in place the balloon was inflated with 20 to 35 ml of saline to a LVEDP of 5 to 15 mm Hg When a stable baseline was achieved 2 5 mg per kilogram of pentazocine was injected intravenously The arterial inflow pump was continuously adjusted so that a constant aortic pressure of 75 mm Hg was maintained Variations in arterial inflow were recorded and the arterial pump calibrated at the end of each experiment Peripheral vascular resistance (PVR) in resistance units was calculated by the expression

$$PVR = \frac{\text{mean aortic pressure}}{\text{mean systemic flow}}$$

High speed tracings were obtained at 5 minute intervals for 60 minutes.

Force velocity relationships were determined using the formula

$$\text{Velocity} = \frac{dp/dt}{28l} \text{ and Force} = \frac{1.36\ P\ r_i^2}{(r0^2 - r_i^2)}$$

where the P equals LVP r_i and r0 equal the internal and external ventricular wall radii respectively and the series elastic modulus is assumed to equal 28. These calculations have been presented in detail by others[3] At the conclusion of each experiment the

	LVEDP			CBF			MVO		
	Pre	Post	p	Pre	Post	p	Pre	Post	p
	0 7	6.4 ± 0 7	NS	86.4 ± 25 3	86.4 ± 29.2	NS	5 1 ± 1.5	5.3 ± 1.3	NS
	2.5	5 1 ± 3 7	NS						
	4.2	9 0 ± 4	NS						

...onary blood flow in ml. per minute. MVO₂ = myocardial oxygen consumption in ... c. per minute per 100 gm. left ventricle ... = proba... ...ation, NS = not significant.

The results of the present study are ...nsistent with these clinical findings, but ...so indicate a primary positive inotropic ...fect of pentazocine. While the exact locus ...action remains unclear the effects of ...ntazocine appear to be blocked by pro...anolol. Peripheral vascular resistance was ...nsistently decreased and was not asso...ated with a delayed inotropic effect. That ...e observed inotropic effect is secondary to ...renal release of catecholamines seems ...likely since the drug had a substantial ...otropic effect ... catecholamine depleted ...imals. In addition, pentazocine adminis...ation has been shown not to be associated ...th histamine release.[4] Thus, it would ...pear that the inotropic effect of pentazo...e is at the beta receptor site.

In these experiments, dose was a critical ...tor in determining the effect on myo...dial contractility. Small doses (0.5 to ...mg per kilogram) always produced an ...rease in LV dp/dt max. As the dose was ...ed to 3 to 5 mg per kilogram a depres...t effect was noted in several animals, and ...es in excess of 5 mg per kilogram uni...nly reduced the LV dp/dt max. In ...tion smaller doses were associated with ...orter duration of inotropic effect, in the ...ge of 25 to 30 minutes, whereas doses of ...3 mg per kilogram resulted in increases ...ontractility of 45 to 60 minutes. Coro...y blood flow was not affected by penta...ne.

...ecent studies in normal animals indicate that morphine has a substantial effect on systemic vascular resistance and an indirect salutary effect on myocardial contractility as a result of sympatho-adrenal discharge.[7] However, Lowenstein and co-workers[8] have shown that large doses of morphine (1 mg per kilogram) had no hemodynamic effect on supine normal human subjects, but that patients undergoing aortic valve replacement increased cardiac output and decreased systemic vascular resistance. It is possible that in patients with acquired heart disease morphine acts by stimulation of baroreceptors leading to compensatory adrenergic discharge. Others have shown a fall in systemic arterial blood pressure in 50 per cent of patients given morphine following myocardial infarction.[9] Pentazocine however has a positive inotropic effect, and causes only transient alterations in systemic vascular resistance. In addition pentazocine has been shown regularly to cause a rise in the blood pressure of patients with hypotension following acute myocardial infarction.[10] If these experimental data are substantiated in clinical studies, then pentazocine may prove a useful drug to provide analgesia in patients following open heart operations or myocardial infarction.

Summary

To clarify the hemodynamic effects of the newly introduced analgesic, pentazocine 30 dogs were studied with a right heart

Table I Effects of pentazocine on m oc rdial contractility coronary blood flow and myocardial oxyg n con umption

	LVP			DP/DT MAX		
	Pre	Post	p	Pre	Post	p
Group I no drug pretr tment n = 20	85.0 ± 7.0	10? 2 8.5	<0.001	1 720 ± 161	2,510 ± 229	<0.00
Group II pr tr ated with propranolol	40 1 ± 11 2	4 9 ± 11 7	NS	1 022 ± 323	1 151 ± 378	NS
Group III pr treat d with reserpine	1?? ± 27.3	60.5 ± 33 7	<0 05	479 ± 260	661 ± 330	<0 01

Abbreviations: LVP = left ventricular pres in mm Hg DP DT MAX = fi st derivative of left ventricular pressure in mm. Hg per secon ... control period before pent zocine dministration; post = maximum response after pentazoci...

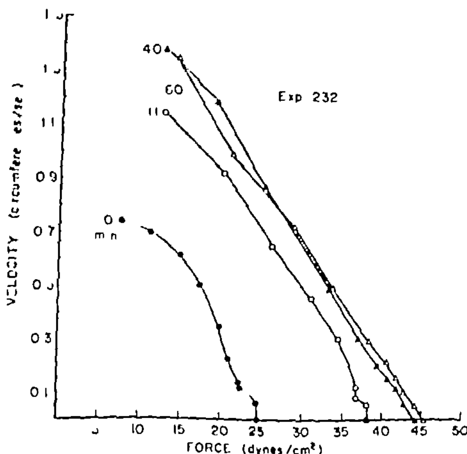


Fig 2 Representative left ventricular force velocity curves obtained under control cond tions (0 min.) nd at 11 40 and 60 minutes after the administration of pentazocine (2.5 mg per kilogram) The shift of the c rve to the right indicates an incre se in contractility

or with nitrous oxide for surgical anesthesia However, a persistent fall in systolic blood pressure w s noted at doses exceeding 5 mg per kilogram Several other groups describe a tendency for the blood pressure to rise after pentazocine administration but d not supply supporting quantitative data In none of these studies has the mechanism for this rise in blood pressure been dated

LVEDP			*CBF*			*MVO*		
Pre	*Post*	*p*	*Pre*	*Post*	*p*	*Pre*	*Post*	*p*
6.8 ± 0.7	6.4 ± 0.7	NS	86.4 ± 25.3	86.4 ± 29.2	NS	5.1 ± 1.5	5.3 ± 1.3	NS
4.9 ± 2.5	5.1 ± 3.7	NS						
8.7 ± 4.2	9.0 ± 4	NS						

CBF = coronary blood flow in ml. per minute; MVO_2 = myocardial oxygen consumption in c.c. per minute per 100 gm. left ventricle; [illegible] administration; NS = not significant.

The results of the present study are consistent with these clinical findings, but also indicate a primary positive inotropic effect of pentazocine. While the exact locus of action remains unclear, the effects of pentazocine appear to be blocked by propranolol. Peripheral vascular resistance was transiently decreased and was not associated with a delayed inotropic effect. That the observed inotropic effect is secondary to adrenal release of catecholamines seems unlikely since the drug had a substantial inotropic effect in catecholamine depleted animals. In addition, pentazocine administration has been shown not to be associated with histamine release. Thus, it would appear that the inotropic effect of pentazocine is at the beta receptor site.

In these experiments, dose was a critical factor in determining the effect on myocardial contractility. Small doses (0.5 to 2 mg. per kilogram) always produced an increase in LV dp/dt max. As the dose was raised to 3 to 5 mg. per kilogram a depressant effect was noted in several animals, and doses in excess of 5 mg. per kilogram uniformly reduced the LV dp/dt max. In addition, smaller doses were associated with a shorter duration of inotropic effect, in the range of 25 to 30 minutes, whereas doses of 2 to 3 mg. per kilogram resulted in increases in contractility of 45 to 60 minutes. Coronary blood flow was not affected by pentazocine.

Recent studies in normal animals indicate that morphine has a substantial effect on systemic vascular resistance and an indirect salutary effect on myocardial contractility as a result of sympatho-adrenal discharge.[7] However, Lowenstein and co-workers[8] have shown that large doses of morphine (1 mg. per kilogram) had no hemodynamic effect on supine normal human subjects, but that patients undergoing aortic valve replacement increased cardiac output and decreased systemic vascular resistance. It is possible that in patients with acquired heart disease morphine acts by stimulation of baroreceptors leading to compensatory adrenergic discharge. Others have shown a fall in systemic arterial blood pressure in 50 per cent of patients given morphine following myocardial infarction.[10] Pentazocine, however, has a positive inotropic effect, and causes only transient alterations in systemic vascular resistance. In addition, pentazocine has been shown regularly to cause a rise in the blood pressure of patients with hypotension following acute myocardial infarction.[11] If these experimental data are substantiated in clinical studies, then pentazocine may prove a useful drug to provide analgesia in patients following open heart operations or myocardial infarction.

Summary

To clarify the hemodynamic effects of the newly introduced analgesic, pentazocine, 30 dogs were studied with a right heart

Table I Effects of penta ocine on myocardial contractility coronary blood flow and myocardial oxygen consumption

	LVP			DP/DT MAX		
	Pre	*Post*	*p*	*Pre*	*Post*	*p*
Group I no drug pretreatment N = 20	85 0 ± 7 0	109 2 ± 8.5	<0 001	1 720 ± 164	2 540 ± 229	<0 00
Group II pretreated with propranolol	40 1 ± 11 2	42 9 ± 11 7	NS	1 022 ± 323	1 154 ± 378	NS
Group III pretreated with reserpine	49 8 ± 27.3	60.5 ± 33 7	<0 05	479 ± 260	661 ± 330	<0 01

Abbreviations LVP = Left ventricular pressure in mm. Hg DP/DT MAX = first derivative of left ventricular pressure in mm. Hg per seco ability using one-tailed Student t test Pre = control period before pentazocine administration; post = maximum response after pentazoc

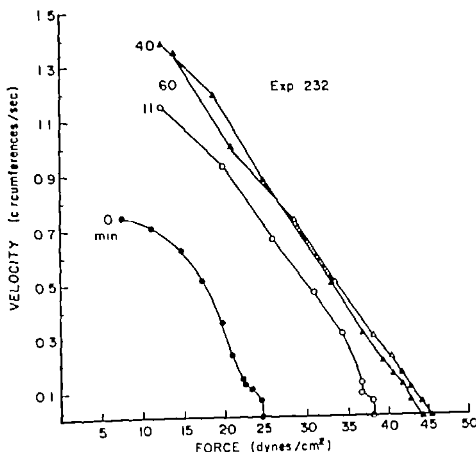


Fig 2 Representative left ventricular force-velocity curves obtained under control conditions (0 min.) and at 11 40 and 60 minutes after the administration of pentazocine (2.5 mg per kilogram) The shift of the curve to the right indicates an increase in contractility

or with nitrous oxide for surgical anesthesia However a persistent fall in systolic blood pressure was noted at doses exceeding 5 mg per kilogram Several other groups describe a tendency for the blood pressure to rise after pentazocine administration but do not supply supporting quantitative data [6] In none of these studies has the mechanism for this rise in blood pressure been elucidated

Case reports

Congenital corrected transposition with atrial inversion and normal hemodynamics

David E. Fixler, Captain, USAF (MC)
Lackland Air Force Base, Texas

Congenital corrected transposition is characterized by transposed great arteries with the systemic venous return directed to the pulmonary artery and the pulmonary venous return directed to the aorta. Complete functional correction of the circulation is rare since most cases are complicated by ventricular septal defects, tricuspid valve anomalies, or pulmonic stenosis. Two anatomic variants of corrected transposition have been described: one with inversion of the ventricles, and the second with inversion of the atria. The latter type is quite uncommon with few cases published in the literature.

The present case is the first reported of congenital corrected transposition with atrial inversion in which the circulation is completely corrected, having normal hemodynamics. A systematic approach to chamber localization in complex morphologic lesions of the heart is reviewed using this case as a model.

Case report

R. H., a 10-year-old boy, was known to have a heart murmur, dextrocardia, and situs inversus since early infancy. His growth and development were normal, and he has had no cardiac symptoms.

Physical examination revealed a healthy-appearing pubescent boy. Blood pressure in the arms was 100/65 and in the left leg 110/68; the pulse was 70. The lungs were clear. No precordial bulge was noted. Cardiac examination revealed no cyanosis or clubbing. A quiet cardiac impulse was palpated in the fifth right intercostal space medial to the midclavicular line. No thrill was palpable. The first heart sound was normal. The second heart sound was single and moderately accentuated at the base. A third heart sound and an ejection systolic click were not heard. A Grade 2/6 short systolic ejection murmur was heard at the upper right sternal border. Diastole was clear. The liver edge was barely palpable at the left costal margin. The pulses were normal.

A chest x-ray (Fig. 1) revealed dextrocardia with situs inversus, no gross cardiac enlargement, normal pulmonary vasculature, and a right aortic arch.

The electrocardiogram (Fig. 2) revealed right axis deviation. The P-wave vector was directed to the right and inferiorly, indicating atrial inversion or a left atrial pacemaker. The presence of a q wave over the left precordium, with a pure R wave in V_{4R}, suggested noninverted ventricles and possible right ventricular hypertrophy. Because of the suspicion of semilunar valve stenosis, cardiac catheterization was performed.

At catheterization the inferior vena cava was on the left and with the superior vena cava drained into the left-sided atrium. Cineangiography revealed that this anatomic right atrium emptied into the left-sided ventricle, which in turn ejected dye into the pulmonary artery (Fig. 3). This ventricular chamber was finely trabeculated and had the contour of a morphologic left ventricle. The ventricular septum was perpendicular to the frontal and coronal planes. On recirculation the pulmonary veins drained into the right-sided atrium. This anatomic "left" atrium emptied into the right-sided ventricle which made up the apex and right heart border. The aortic

From the Department of Pediatrics, Wilford Hall, USAF Medical Center, Lackland Air Force Base, Texas.
Received for publication Jan. 21, [illegible].
Reprint requests to: Department of Pediatrics, Wilford Hall USAF Medical Center, Lackland Air Force Base, Texas 78236.

bypass preparation using an isovolumetric balloon technique Heart rate and coronary artery perfusion pressure were held constant After the rapid intravenous administration of 2 5 mg per kilogram of pentazocine the left ventricular pressure (LVP) increased by 28 per cent LV dp/dt max increased by 46 per cent, and the force velocity curve was shifted upward and to the right indicating a positive inotropic effect. The increase in contractility was noted 5 to 10 minutes after pentazocine injection and was sustained for 45 to 60 minutes. This reaction was blocked by the prior administration of propranolol but was unaffected by previous catecholamine depletion with reserpine. All animals exhibited a transient fall in peripheral vascular resistance of 42 5 per cent within 2 minutes after pentazocine administration but resistance returned to baseline levels within 3 minutes. Coronary blood flow and myocardial oxygen consumption were unaltered These data indicate that pentazocine has a beta stimulating inotropic effect and therefore it may be particularly useful for providing analgesia in patients with impaired myocardial contractility The usefulness of the drug in such patients must, however be assessed in appropriate clinical studies.

REFERENCES

1 Archer S., Albertson N F Harris, L. S et al Narcotic-antagonists as analgesics, Science 137:541 1962
2. Lal, S. Savidge R. S., and Davies, D M Analgesics in myocardial infarction AMER HEART J 79:717 1970.
3 Enright L. P Hannah H and Reis, R. L. Effects of acute regional myocardial ischemia on left ventricular function in dogs, Circ. Res. 26:307 1970.
4 Lal S. Savidge R. S and Chhabra G. P: Cardiovascular and respiratory effects of morphine and pentazocine in patients with myocardial infarction, Lancet 1:379 1969
5 Sadove M Balagot R. C., and Pecora F N: Pentazocine—a nonaddicting analgesic, J.A.M.A. 189:199 1964
6. Ahlgren, E. W and Stephen C. R. Laboratory and clinical experience with a new analgesic pentazocine, Anesth Analg 45:673 1966.
7 Vasko, J S. Henney R. P., Brawley R. K., et al. Effects of morphine on ventricular function and myocardial contractile force Amer J Physiol 210:329 1966
8. Henney R. P Vasko J S Brawley R. K., et al The effects of morphine on the resistance and capacitance vessels of the peripheral circulation, AMER. HEART J 72:242 1966.
9 Lowenstein E., Hallowell P Levine, F H et al: Cardiovascular response to large doses of intravenous morphine in man, New Eng J Med 281:1389 1969
10 Scott, M E. and Orr R: Effects of diamorphine methadone morphine and pentazocine in patients with suspected acute myocardial infarction Lancet 1:1065 1969

Case reports

Congenital corrected transposition with atrial inversion and normal hemodynamics

David E. Fixler Captain USAF (MC)
Lackland Air Force Base Texas

Congenital corrected transposition is characterized by transposed great arteries with the systemic venous return directed to the pulmonary artery and the pulmonary venous return directed to the aorta. Complete functional correction of th circulation is rare since most cases are complicated by ventricular septal defects, tricuspid valve anomalies or pulmonic stenosis. Two anatomic variants of corrected transposition have been described one with inversion of the ventricles, and the second with inversion of the atria. The latter type is quite uncommon with few cases published in the literature

The present case is the first reported of congenital corrected transposition with atrial inversion in which the circulation is completely "corrected having normal hemodynamics. A systematic approach to chamber localization in complex morphologic lesions of the heart is reviewed using this case as a model

Case report

R H 10-year-old boy was known to have heart murmur dextrocardia, and situs inversus since early infancy His growth nd development ere normal, nd he has had no cardiac symptoms.

Physical examination revealed healthy-appearing pubescent boy Blood pressure in the arms was 100/63 nd in the left leg 110/68 the pulse was 70 The lungs ere clear N precordial bulge was noted. Cardiac examination revealed no cyanosis or clubbing A quiet cardiac impulse was palpated | the fifth right intercostal space medial to the midclavicular line. No thrill was palpable. The first heart sound was normal. The second heart sound w single nd moderately accentuated at the base. A third heart sound nd an ejection systolic click ere not heard. A Grade 2/6 short systolic ejection murmur was heard t the upper right sternal border *Diastole* was clear The liver edge was barely palpable t the left costal margin. The pulses were normal.

A chest -ray (Fig 1) revealed dextrocardia with situs inversus, no gross cardiac enlargement, normal pulmonary vasculature, and right aortic arch.

The electrocardiogram (Fig. 2) revealed right axis deviation. The P wave vector was directed to the right and inferiorly indicating atrial inversion or a left trial pacemaker The presence of q wave over the left precordium, with pure R wave in V_{4R}, suggested noninverted ventricles and possible right ventricular hypertrophy Because of the suspicion of semilunar valve stenosis, cardiac catheterization was performed.

At catheterization the inferior vena cava was on the left nd with the superior vena cava drained into the left-sided atrium. Cineangiography revealed that this anatomic right atrium emptied into the left-sided ventricle, hich in turn ejected dye into the pulmonary artery (Fig 3). This ventricular chamber was finely trabeculated and had the contour of morphologic left ventricle. The ventricular septum was perpendicular to the frontal nd coronal planes. On recirculation the pulmonary veins drained into the right-sided atrium. This anatomic "left trium emptied into the right-sided ventricle which made up the apex and *right* heart border The aortic

From the Department of Pediatrics, Wilford Hall, USAF Medical Center, Lackland Air Force Base Texas.
Received for publication Jan. 28 1970.
Reprint requests to: Department of Pediatrics, Wilford Hall USAF Medical Center Lackland Air Force Base, Texas 78236.

Vol. 81 No. 3 pp. 387-391 March, 1971



Fig *1* Frontal chest roentgenogram Note dextrocardia right aortic arch, and right sided ga tric s lhouette

valve was to the right of the pulmonic lve The ascending aorta coursed parallel to the ma pulmonary artery and arched to the right In the later l projection the two ventricles overlay one nother with the right ventricular outflow tract being an te rior The aortic valve wa anterior and cephalad to the pulmonic valve indicating tran posit on of the great arteries. A right ventricul r cine ngiogram w not performed because of the recurring ventricular extrasystoles with the catheter in th ch mber The pressure tracings fa led to demon tr ite ny ignifi cant valvar obstruction (Table I) No sh nt w detected by the oxygen saturation dat Dye-d lut on curves (injecting left ventricle sampling orta) failed to reveal evidence of a shunt or A V valve insuf ficiency The diagnosis was dextrocardia situs inversus with atrial inversion and D-transposition of the great arteries (D bulboventricular loop)

Discussion

The case presented is one of the rarest types of transposition of the great arteries [1] In many complex cases accurate deter mination of the chamber arrangement is difficult A systematic approach has been proposed to facilitate precise anatomical diagnosis which is based upon (1) the rela tionship of the viscera and atria (visceral situs), (2) the relationship of the

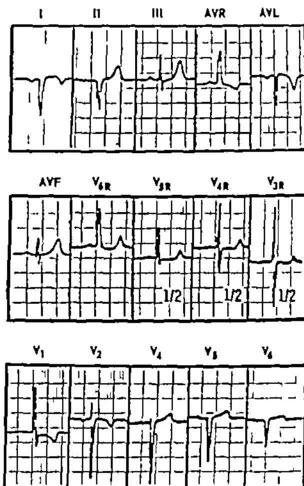


Fig *2* Electrocardiog am Note negative P waves in Lead I aV$_1$ and V$_6$. Presence of q waves in V$_{4-6}$ s ggests noni verted ventricles.

Table I Cardiac catheterization data

Locati n	*O saturation ( )*	*Pressure (mm Hg)*
SVC	83	
IVC	88	
Morphologic RA	81	A = 5 V = 3 M = 4
LV (Subp lmonic ventr cle)	82	25/0 − 5
RV (Subaortic ve tricle)		95/0 − 8
Aort	96	95/62 M = 81

and (3) the relationship of the great arteries.[3]

The visceral situs is commonly deter mined roentgenographically by observing the location of the liver and gastric bubble

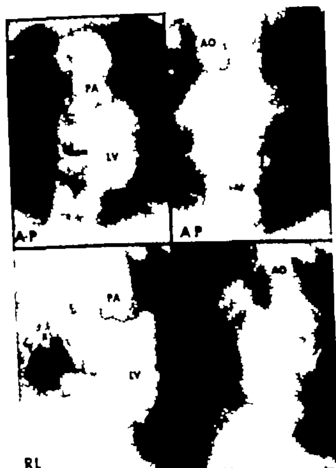


Fig. 3 Single cineangiographic frames showing relationships of the ventricles and great arteries. *PA* = P l- monary artery *LV* = left entricle *AO* = aorta. Positions of pulmonic nd aortic valves are outlined for clarity

the visceral arrangement may be deter mined by gastrointestinal studies localizing the stomach and cecum Three types of visceral relationships are possible (1) situs solitus, the normal condition, in which the liver and cecum lay on the right, the stomach on the left (2) situs inversus, the reverse cond tion, in which the liver and cecum lay on the left, the stomach on the right (3) situs symmetricus the indeter minate condition in which the liver cecum and stomach assume a midline position. In the first two conditions the visceral situs and atrial situs are almost always the same i.e., with visceral inversion (situs inversus) the atria are invariably inverted There fore roentgenographically the atrial loca tions frequently may be predicted prior to catheterization. In situs symmetricus how ever the continuity between the inferior vena cava and anatomic right atrium is a more reliable guide for atrial identification than the visceral situs. [3] Unfortunately the inferior vena cava is usually not localized until cardiac catheterization or autopsy has been performed

The ventricular relationship is often re flected in the QRS progression in the pre cordial leads. Portillo and associates have shown that rS or RS patterns are more often recorded over the right ventricle whereas qRs or QR patterns are seen over the left ventricle. When a left ventricular pattern is recorded in the right precordial leads ventricular inversion should be suspected. However severe right ventricular hy pertrophy may produce qR patterns over the right ventricle thereby making the electrocardiogram less reliable for ven tricular localization

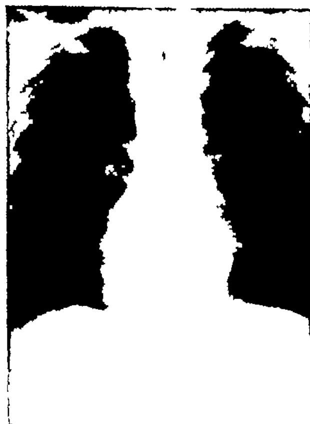


Fig. 1. Frontal chest roentgenogram. Note dextrocardia, right aortic arch, and right-sided gastric silhouette.

valve was to the right of the pulmonic valve. The ascending aorta coursed parallel to the main pulmonary artery and arched to the right. In the lateral projection the two ventricles overlay one another with the right ventricular outflow tract being anterior. The aortic valve was anterior and cephalad to the pulmonic valve, indicating transposition of the great arteries. A right ventricular cineangiogram was not performed because of the recurring ventricular extrasystoles with the catheter in this chamber. The pressure tracings failed to demonstrate any significant valvar obstruction (Table I). No shunt was detected by the oxygen saturation data. Dye-dilution curves (injecting left ventricle, sampling aorta) failed to reveal evidence of a shunt or AV valve insufficiency. The diagnosis was dextrocardia situs inversus with atrial inversion and D-transposition of the great arteries (D-bulboventricular loop).

Discussion

The case presented is one of the rarest types of transposition of the great arteries.[1] In many complex cases accurate determination of the chamber arrangement is difficult. A systematic approach has been proposed to facilitate precise anatomical diagnosis which is based upon (1) the relationship of the viscera and atria (visceral atrial situs), (2) the relationship of the ventricles (type of bulboventricular loop)

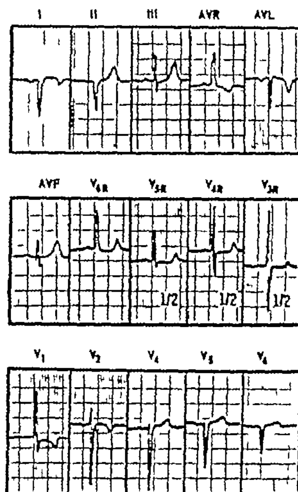


Fig. 2. Electrocardiogram. Note negative P waves in Leads I, aVL, and V6. Presence of q waves in V4-6 suggests noninverted ventricles.

Table I. Cardiac catheterization data

Location	O_2 saturation (%)	Pressure (mm Hg)
SVC	83	
IVC	88	
Morphologic RA	81	A = 5 V = 3 M = 4
LV (Subpulmonic ventricle)	81	25/0 – 5
RV (Subaortic ventricle)		95/0 – 8
Aorta	96	95/6_, M = 84

and (3) the relationship of the great arteries.[2]

The visceral situs is commonly determined roentgenographically by observing the location of the liver and gastric bubble on routine chest x-ray. In unclear situations



Fig. 3. Single cineangiographic frames showing relationships of the entricles nd great arteries. *PA* = Pulmonary artery *LV* = left ventricle *AO* = orta. Positions of pulmonic and ortic valves are outlined for clarity

the visceral arrangement may be deter mined by gastrointestinal studies localizing the stomach and cecum Three types of visceral relationsh ps are possible (1) situs solitus, the normal condition in which the liver and cecum lay on the right, the stomach on the left (2) situs inversus the reverse condition, in which the liver and cecum lay on the left, the stomach on the right (3) situs symmetricus, the indeter minate condition in which the liver cecum and stomach assume a midline position In the first two conditions the visceral situs and atrial situs are almost always the same i.e., w th visceral inversion (situs inversus) the atria are invariably inverted There fore, roentgenographically the atrial loca tions frequently may be predicted prior to catheterization In situs symmetricus how ever the continu ty between the inferior vena cava and anatomic right atrium is a more reliable guide for atrial identification than the visceral situs.[4,6] Unfortunately the inferior vena cava is usually not localized until cardiac catheterization or autopsy has been performed

The ventricular relationship is often re flected in the QRS progression in the precordial leads. Portillo and associates[4] have shown that rS or RS patterns are more often recorded over the right ventricle whereas qRs or QR patterns are seen over the left ventricle When a left ventricular pattern is recorded in the right precordial leads, ventricular inversion should be suspected. However severe right ventricular hy pertrophy may produce qR patterns over the right ventricle thereby making the electrocardiogram less reliable for ven tricular localization.

Cardiac catheterization remains the best method of determining ventricular and great vessel relationships. From selective angiocardiograms the ventricles frequently can be identified by their characteristic trabeculations and contours. Van Praagh and co-workers[3] have emphasized that the relationship of the great arteries identifies the underlying ventricles. Generally, when the aortic valve lies to the right of the pulmonic valve, a d-loop is present, signifying that the morphologic right ventricle is right-sided. Conversely, when the aortic valve lies to the left of the pulmonic valve, an l-loop is present, indicating that the right ventricle lies to the left of the morphologic left ventricle (ventricular inversion). In Van Praagh's[3] extensive series the relationship of the semilunar valves indicated the type of cardiac loop correctly in 95 per cent of the cases.

The clinical findings in the present case are similar to other reported cases of corrected transposition having no associated cardiac malformations.[8,11] Since hemodynamic abnormalities are absent, symptoms do not occur unless secondary to arrhythmias. Unfortunately, varying degrees of heart block frequently accompany corrected transposition. Berry and associates[12] report 4 out of 13 cases and Anderson and co-workers[13] 3 out of 17 cases with second degree or complete heart block. Characteristically, a loud single second heart sound is heard originating from the transposed aortic valve. This may be misinterpreted as indicating pulmonary hypertension. Loud systolic murmurs commonly occur in corrected transposition with the frequent accompaniment of ventricular septal defects and tricuspid insufficiency. From 2 reports representing 57 cases of corrected transposition, over 90 per cent had either ventricular septal defects or tricuspid regurgitation.[11,13]

Circulation through the heart is schematically shown in Fig. 4. The systemic venous atrium (morphologic right atrium) lies on the left and drains into the morphologic left ventricle, presumably through a mitral valve. This left ventricle ejects blood into the pulmonary artery. The pulmonary venous drainage enters the right-sided atrium (morphologic left atrium) and

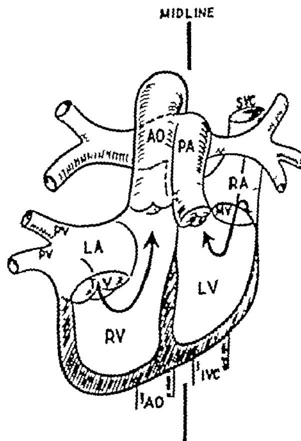


Fig. 4. Relationship of the cardiac chambers and great vessels as interpreted from the cardiac catheterization findings. Atrioventricular valves are presumed to follow their underlying ventricles.

crosses a presumed tricuspid valve into the morphologic right ventricle. The right ventricle in turn ejects into the transposed aorta. No intracardiac defect is present. This heart may be viewed as a true mirror image of the more common form of corrected transposition, i.e., levocardia, situs solitus, l-loop, and l-transposition. The presence of atrial inversion with transposition functionally corrects the circulation. This case represents a natural hemodynamic model of the popular atrial baffle procedure proposed by Mustard and co-workers[14] in which the venous returns are surgically inverted. The long term prognosis remains guarded since it cannot be predicted if arrhythmias will occur and it is not known whether the tricuspid valve and anatomic right ventricle will continue to function normally under a constant systemic pressure load.

Summary

The first reported case of corrected transposition with atrial inversion and normal

hemodynamics is presented. The patient is an asymptomatic 10-year-old boy with a loud single second heart sound and a soft systolic ejection murmur at the base. The electrocardiogram reveals a P wave vector directed to the right and inferiorly suggesting atrial inversion. The presence of q waves in V_{1-4} suggests noninverted ventricles. Chest roentgenograms show dextrocardia situs inversus, and a right aortic arch. Cardiac catheterization hemodynamic data reveal no evidence of a shunt or significant valvar abnormalities. On angiography the aortic valve lies to the right of the pulmonic valve and is more cephalad indicating D transposition of the great arteries. The circulation is functionally completely corrected since the systemic venous drainage enters the left-sided atrium and is ejected into the pulmonary artery by the left ventricle. The pulmonary venous drainage enters the right-sided atrium and is ejected into the transposed aorta by the right ventricle.

A systematic approach to chamber localization is reviewed based upon (1) the relationship of the viscera and atria (visceral atrial situs) (2) the relationship of the ventricles (type of bulboventricular loop) (3) the relationship of the great arteries.

The author would like to thank Dr. Alexander J. Muster of The Children's Memorial Hospital, Chicago, Ill. for his critical review of the manuscript.

REFERENCES

1. Ruttenberg, H. D.: Corrected transposition of the great vessels, *In* Moss, A. J., and Adams, F. H., editors: Heart disease in infants, children and adolescents, Baltimore, 1968, The Williams & Wilkins Company, p. 556.
2. Gasul, B. M., Arcilla, R. A., and Lev, M.: Heart disease in children, Philadelphia, 1966, J. B. Lippincott Company, p. 1001.
3. Van Praagh, R., Van Praagh, S., Vlad, P., and Keith, J. D.: Anatomic types of congenital dextrocardia, Amer. J. Cardiol. 13:510, 1964.
4. Hastreiter, A. R., and Rodriguez-Coronel, A.: Discordant situs of thoracic and abdominal viscera, Amer. J. Cardiol. 22:111, 1968.
5. Lev, M., Liberthson, R. R., Eckner, F. A. O., and Arcilla, R. A.: Pathologic anatomy of dextrocardia and its clinical implications, Circulation 37:979, 1968.
6. Portillo, B., Anselmi, G., Sod' Pallares, D., and Medrano, G. A.: Importance of the unipolar leads in the diagnosis of dextrocardias, levocardias, dextropositions, and dextrorotations, Amer. Heart J. 57:396, 1959.
7. Van Praagh, R.: Chamber localization, *In* Keith, J. D., Rowe, R. D., and Vlad, P., editors: Heart disease in infancy, New York, 1968, The Macmillan Company, p. 792.
8. Walmsley, T.: Transposition of the ventricles and arterial stems, J. Anat. 65:528, 1931.
9. Edwards, J. E., Dry, T. J., Parker, R. L., Burchell, H. B., Wood, E. H., and Bulbulian, A. H.: Atlas of congenital anomalies of the heart and great vessels, Springfield, Ill., 1954, Charles C Thomas, Publisher, p. 104.
10. Schiebler, J. A., and Rudolph, L. A.: Corrected transposition of the great vessels, Amer. Heart J. 54:610, 1957.
11. Cumming, G. R.: Congenital corrected transposition of the great vessels without associated intracardiac anomalies: A clinical hemodynamic and angiocardiographic study, Amer. J. Cardiol. 10:605, 1962.
12. Berry, W. B., Roberts, W. C., Morrow, A. G., and Braunwald, E.: Corrected transposition of the aorta and pulmonary trunk, Amer. J. Med. 36:35, 1964.
13. Anderson, R. C., Lillehei, C. W., and Lester, R. G.: Corrected transposition of the great vessels of the heart: A review of 17 cases, Pediatrics 20:626, 1957.
14. Schiebler, G. L., Edwards, J. E., Burchell, H. B., DuShane, J. W., Ongley, P. A., and Wood, E. H.: Congenital corrected transposition of the great vessels. A study of 33 cases, Pediatrics 27(Suppl.):849, 1961.
15. Fontana, R. S., and Edwards, J. E.: Congenital cardiac disease: A review of 357 cases studied pathologically, Philadelphia, 1962, W. B. Saunders Company, p. 291.
16. Mustard, W. T., Keith, J. D., Trusler, G. A., Fowler, R., and Kidd, L.: The surgical management of transposition of the great vessels, J. Thorac. Cardiovasc. Surg. 48:953, 1964.

Cardiac catheterization remains the best method of determining ventricular and great vessel relationships. From selective angiocardiograms the ventricles frequently can be identified by their characteristic trabeculations and contours. Van Praagh and co-workers[3] have emphasized that the relationship of the great arteries identifies the underlying ventricles. Generally, when the aortic valve lies to the right of the pulmonic valve, a d loop is present, signifying that the morphologic right ventricle is right-sided. Conversely, when the aortic valve lies to the left of the pulmonic valve, an l loop is present, indicating that the right ventricle lies to the left of the morphologic left ventricle (ventricular inversion). In Van Praagh's[7] extensive series the relationship of the semilunar valves indicated the type of cardiac loop correctly in 95 per cent of the cases.

The clinical findings in the present case are similar to other reported cases of corrected transposition having no associated cardiac malformations.[8-11] Since hemodynamic abnormalities are absent, symptoms do not occur unless secondary to arrhythmias. Unfortunately, varying degrees of heart block frequently accompany corrected transposition. Berry and associates[12] report 4 out of 13 cases, and Anderson and co-workers[13] 3 out of 17 cases with second degree or complete heart block. Characteristically, a loud single second heart sound is heard originating from the transposed aortic valve. This may be misinterpreted as indicating pulmonary hypertension. Pansystolic murmurs commonly occur in corrected transposition with the frequent accompaniment of ventricular septal defects and tricuspid insufficiency. From 2 reports representing 57 cases of corrected transposition, over 90 per cent had either ventricular septal defects or tricuspid regurgitation.[11,14]

Circulation through the heart is schematically shown in Fig. 4. The systemic venous atrium (morphologic right atrium) lies on the left and drains into the morphologic left ventricle, presumably through a mitral valve. This left ventricle ejects blood into the pulmonary artery. The pulmonary venous drainage enters the right-sided atrium (morphologic left atrium) and crosses a presumed tricuspid valve into the morphologic right ventricle. The right ventricle in turn ejects into the transposed aorta. No intracardiac defect is present. This heart may be viewed as a true mirror image of the more common form of corrected transposition, i.e., levocardia, situs solitus, l loop, and l transposition. The presence of atrial inversion with transposition functionally corrects the circulation. This case represents a natural hemodynamic model of the popular atrial baffle procedure proposed by Mustard and co-workers[15] in which the venous returns are surgically inverted. The long term prognosis remains guarded since it cannot be predicted if arrhythmias will occur and it is not known whether the tricuspid valve and anatomic right ventricle will continue to function normally under a constant systemic pressure load.

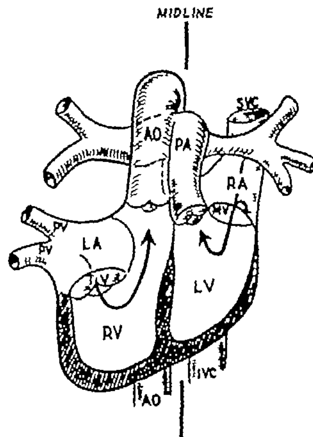


Fig. 4. Relationship of the cardiac chambers and great vessels as interpreted from the cardiac catheterization findings. Atrioventricular valves are presumed to follow their underlying ventricles.

Summary

The first reported case of corrected transposition with atrial inversion and normal

hemodynamics is presented The patient is an asymptomatic 10-year-old boy with a loud single second heart sound and a soft systolic ejection murmur at the base. The electrocardiogram reveals a P wave vector directed to the right and inferiorly sug gesting atrial inversion The presence of q waves in V_4 suggests noninverted ventricles. Chest roentgenograms show dextrocardia situs inversus, and a right aortic arch. Cardiac catheterization hemodynamic data reveal no evidence of a shunt or sig nificant valvar abnormalities. On angiog raphy the aortic valve lies to the right of the pulmonic valve and is more cephalad indicating D transposition of the great arteries. The circulation is functionally completely corrected since the systemic venous drainage enters the left-sided atrium and is ejected into the pulmonary artery by the left ventricle. The pulmonary venous drainage enters the right-sided atrium and is ejected into the transposed aorta by the right ventricle.

A systematic approach to chamber locali zation is reviewed based upon (1) the rela tionship of the viscera and atria (visceral atrial situs) (2) the relationship of the ventricles (type of bulboventricular loop) (3) the relationship of the great arteries.

The author would like to thank Dr Alexander J Muster of The Children Memorial Hospital, Chicago, Ill for his critical review of the manuscript.

REFERENCES

1. Ruttenberg H. D Corrected transposition of the great vessels, Moss, A. J and Adams, F H., editors Heart disease in infants, children and adolescents, Baltimore, 1969 The Williams & Wilkins Company p. 556.
2. Gasul, B M Arcilla, R. A., and Lev M. Heart disease in children, Philadelphia 1966 J B. Lippincott Company p. 1001.
3. Van Praagh, R., Van Praagh, S Vlad, P and Keith, J D Anatomic types of congenital dextrocardia, Amer J Cardiol. 13:510, 1964
4. Hastreiter A. R., and Rodriguez-Coronel, A.: Discordant situs of thoracic and abdominal viscera, Amer J Cardiol. 22 111 1968.
5. Lev M Liberthson, R. R., Eckner F A. O and Arcilla, R. A. Pathologic anatomy of dextrocardia and its clinical implications, Circulation 37:979 1968.
6. Portillo, B Anselmi, G., Sodi-Pallares, D and Medrano, G. A.: Importance of the unipolar leads in the diagnosis of dextrocardias, levocardias, dextropositions, and dextrorotations, Amer. Heart J 57:396, 1959
7. Van Praagh R. Chamber localization, *in* Keith J D Rowe, R. D and Vlad, P., editors. Heart disease in infancy New York, 1968, The Macmillan Company p. 792.
8. Walmsley T: Transposition of the ventricles and arterial stems, J Anat. 65:528, 1931
9. Edwards, J E., Dry T J Parker R. L., Burchell, H. B., Wood, E. H., and Bulbulian, A. H.: Atlas of congenital anomalies of the heart and great vessel Springfield, Ill., 1954 Charles C Thomas, Publisher p. 104.
10. Schaefer J A., and Rudolph L. A.: Corrected transposition of the great vessels, Amer. Heart J 54:610, 1957
11. Cumming, G. R.: Congenital corrected transposition of the great vessels without associated intracardiac anomalies A clinical, hemodynamic and angiocardiographic study Amer J Cardiol. 10:605 1962.
12. Berry W B Roberts, W C., Morrow A. G., and Braunwald, E. Corrected transposition of the aorta and pulmonary trunk, Amer J Med. 36:35 1964.
13. Anderson, R. C., Lillehei, C. W and Lester R. G. Corrected transposition of the great vessels of the heart: A review of 17 cases, Pediatrics 20:626, 1957
14. Schiebler G. L., Edwards, J E., Burchell, H. B DuShane, J W Ongley P A and Wood, E. H.: Congenital corrected transposition of the great vessels: A study of 33 cases, Pediatrics 27(Suppl.) 849 1961.
15. Fontana, R. S., and Edwards, J E. Congenital cardiac disease: review of 357 cases studied pathologically Philadelphia, 1962, W B Saunders Company p. 291
16. Mustard, W T Keith, J D Trusler G. A., Fowler R., and Kidd, L. The surgical management of transposition of the great vessels, J Thorac. Cardiovasc. Surg. 48:953 1964.

Annular subvalvular left ventricular aneurysm in a North American infant

*Gordon M Folger Jr M D**
Paul E Stanton M D
Augusta Ga

An unusual form of left ventricular aneurysm in which single or multiple sacs arose directly adjacent to the fibrous ring of the mitral or aortic valve was recently described in Nigerian natives by Robertson and Jackson[1] and Abrahams and associates[2] and has been termed annular subvalvular left ventricular aneurysm A review of the previous literature has disclosed similar cardiac aneurysms of unknown etiology[3-9] and more recently additional cases have been described[10-13] The age range of these previous cases has been 5 to 45 years and a congenital origin has been suggested[2]

It is the purpose of this paper to present the case of a 6-month-old infant who reveals clinical findings compatible with the diagnosis of annular subvalvular left ventricular aneurysm To our knowledge this is the youngest recorded instance of this condition

Case report

A. H (ETMH No. 088-169) a 6-month-old Negro female infant was admitted to the teaching hospital of the Medical College of Georgia on Sept 26 1967 Neonatal history revealed that the infant had poor weight gain in the first 2 months of life and that she had become quite fretful after taking small amount of feeding At age 3 months, the patient was noted to have the onset of grand mal type seizures, occurring daily necessitating consultation at a local hospital where medication with phenobarbital was begun A chest radiogram taken at that time revealed enlargement of the heart and the electrocardiogram showed a pattern interpreted as anterior myocardial ischemia The infant improved on phenobarbital although she did continue to have 2 or more episodes of brief staring type seizures daily unassociated with any other central nervous system symptoms Because of her suspected cardiac disease she was referred to the Medical College of Georgia.

Physical examination on admission revealed a healthy infant whose height and weight were within the fiftieth percentile The respiratory rate was 30 per minute the pulse 110 per minute and blood pressure 108/82 mm. Hg There was a soft Grade 2/6 systolic ejection type murmur heard best along the lower left sternal border with radiation to the apex The first heart sound was muffled and the second sound was prominent and split The remainder of the physical examination was within normal limits. Chest radiograms (Fig 1) revealed the heart to be enlarged with upward tilting of the apex. A rounded bulge on the superior anterolateral aspect of the left ventricle was present demonstrating reduced contraction on fluoroscopy The pulmonary vasculature was normal. The electrocardiogram (Fig 2 4) confirmed the previous findings indicative of anterior myocardial ischemia. The vectorcardiogram (Fig 3) showed lack of closure of the QRS loop indicating an S-T vector whose spatial direction was

From the Department of Pediatrics, Medical College of Georgia, Eugene Talmadge Memorial Hospital, Augusta, Ga.
Supported in part by National Institutes of Health Grant 2T1HE5442 09
Received for publication Jan. 30, 1970.
Reprint requests to Gordon M Folger J M.D Department of Pediatrics, Section of Pediatric Cardiology Medical College of Georgia, Eugene Talmadge Memorial Hospital, Augusta, Ga. 30902.
*Associate Professor of Pediatrics; Director Section of Pediatric Cardiology Medical College of Georgia, Augusta, Ga.

oriented to the left, superiorly and posteriorly. Voltage of the Q and R vectors was normal. The vertical position of the loop in the frontal plane helped explain the narrow loop in the horizontal plane which was viewed on edge. The ordinary criteria for myocardial infarction were absent, but an intraventricular conduction defect was present which did not resemble block of either His bundle. QRS (92 msec.) was outside the ninety-fifth percentile for this age. The delay was accounted for mostly by slowing in the initial segment (slurred first 26 msec.) and suggested intra-infarction block. This term implies the circuitous (and thereby slow) excitation of normal muscle within an area interspersed with electrically inert (i.e., fibrous) tissue.

Data obtained at cardiac catheterization revealed normal right heart pressures. Oxygen saturations demonstrated no evidence of intracardiac shunting. The aortic and left ventricular pressures were within the limits of normal showing only the usual slight elevation of the end-diastolic pressure in the left ventricle following the use of contrast material for angiography. A cineaortagram performed with the catheter in the supravalvular aortic position revealed opacification of the coronary arteries in the normal sequence. The left coronary artery was slightly higher than the right, and the circumflex branch appeared somewhat tortuous over the anterolateral aspect of the left ventricle. There was no obstruction or dilatation of the coronary vessels. A cineangiocardiogram in the frontal plane with the catheter in the left ventricle showed a normal-sized chamber with good contractions and normal outflow tract. There was a constant defect which opacified in the superior anterolateral left ventricular myocardium over which the tortuous circumflex coronary artery appeared to pass. Left ventricular angiography with the patient in the right anterior oblique projection (Fig. 4) showed the area of opacity in the left ventricular myocardium to communicate with the left ventricle by a single narrow sinusoidal channel. This channel appeared to arise near the anterior aspect of the mitral valve annulus. The aneurysmal space emptied readily into the left ventricle with systole although contraction in this area appeared reduced. This systolic emptying is interpreted as indicating an effective myocardial mass surrounding the aneurysm. There was no evidence of mitral regurgitation. The angiocardiogram of the right ventricle was normal. The diagnosis was annular subvalvular left ventricular aneurysm arising from the mitral valve.

Twenty-seven months after her initial visit, the patient is without symptoms and positive cardiac findings. The chest radiograms have shown no change. The electrocardiogram, however, shows significant improvement principally in regard to the ST-T changes seen earlier (Fig. 2, *B*). Due to the stable cardiac condition, surgery has not been advised.

Discussion

This patient is considered to have findings ... as well as angiographic, characteristic of those reported with annular subvalvular left ventricular aneurysm involving the mitral valve. The electrocardiographic findings together with the reported symptomatology and the patient's age made necessary the exclusion of an anomalous left coronary artery arising from the pulmonary artery. Other conditions of the coronary arteries in infancy such as early calcification in addition to primary myocardial disorders, although unlikely, required elimination as etiologic possibilities. With the diagnosis, as proven by selective cineangiocardiography, a developmental origin of this abnormality is indicated although not proven.

Forms of left ventricular aneurysms of a congenital nature that have been described include ventricular diverticulae and aneurysms associated with anomalous origin of the left coronary artery. Diverticulae may be distinguished from the entity under discussion principally by their anatomic location at the apex of the heart. Aneurysmal dilatation of the left ventricle is common with an anomalous origin of the left coronary artery but discreet aneurysms such as seen in our patient do not occur. The clinical findings in our case are similar to those cases previously described[1, 4-9] in which an unusual form of left ventricular aneurysm was found which seemed to differ from the afore



Fig. 1. Frontal chest radiogram. The heart is moderately enlarged with uptilting of the apex. The area between arrows represents the position of the aneurysm as defined by the left ventricular angiograms performed in the frontal projection.

Annular subvalvular left ventricular aneurysm in a North American infant

*Gordon M. Folger, Jr., M.D.**
Paul F. Stanton, M.D.
Augusta, Ga.

An unusual form of left ventricular aneurysm in which single or multiple sacs arose directly adjacent to the fibrous ring of the mitral or aortic valve was recently described in Nigerian natives by Robertson and Jackson[1] and Abrahams and associates[2] and has been termed annular subvalvular left ventricular aneurysm. A review of the previous literature has disclosed similar cardiac aneurysms of unknown etiology,[3-5] and more recently additional cases have been described.[6-11] The age range of these previous cases has been 5 to 45 years, and a congenital origin has been suggested.[2]

It is the purpose of this paper to present the case of a 6-month-old infant who reveals clinical findings compatible with the diagnosis of annular subvalvular left ventricular aneurysm. To our knowledge this is the youngest recorded instance of this condition.

Case report

A. H. (ETMH No. 088-169) a 6-month-old Negro female infant, was admitted to the teaching hospital of the Medical College of Georgia on Sept. 26, 1967. Neonatal history revealed that the infant had poor weight gain in the first 2 months of life and that she had become quite fretful after taking small amounts of feeding. At age 3 months, the patient was noted to have the onset of grand mal type seizures, occurring daily, necessitating consultation at a local hospital where medication with phenobarbital was begun. A chest radiogram taken at that time revealed enlargement of the heart, and the electrocardiogram showed a pattern interpreted as anterior myocardial ischemia. The infant improved on phenobarbital although she did continue to have 2 or more episodes of brief staring type seizures daily unassociated with any other central nervous system symptoms. Because of her suspected cardiac disease she was referred to the Medical College of Georgia.

Physical examination on admission revealed a healthy infant whose height and weight were within the fiftieth percentile. The respiratory rate was 30 per minute, the pulse 110 per minute, and blood pressure 108/82 mm. Hg. There was a soft Grade 2/6 systolic ejection type murmur heard best along the lower left sternal border with radiation to the apex. The first heart sound was muffled and the second sound was prominent and split. The remainder of the physical examination was within normal limits. Chest radiograms (Fig. 1) revealed the heart to be enlarged with upward tilting of the apex. A rounded bulge on the superior anterolateral aspect of the left ventricle was present demonstrating reduced contraction on fluoroscopy. The pulmonary vasculature was normal. The electrocardiogram (Fig. 2, A) confirmed the previous findings indicative of anterior myocardial ischemia. The vectorcardiogram (Fig. 3) showed lack of closure of the QRS loop indicating an S-T vector whose spatial direction was

From the Department of Pediatrics, Medical College of Georgia, Eugene Talmadge Memorial Hospital, Augusta, Ga.

Supported in part by National Institutes of Health Grant 2T1HE5412-09.

Received for publication Jan. 30, 1970.

Reprint requests to: Gordon M. Folger, Jr., M.D., Department of Pediatrics, Section of Pediatric Cardiology, Medical College of Georgia, Eugene Talmadge Memorial Hospital, Augusta, Ga. 30902.

*Associate Professor of Pediatrics, Director, Section of Pe[illegible] [illegible], Medical College of Georgia, Augusta, Ga.

Three patients reacted with slight hypotension which in 2 cases, was treated with metaraminol intramuscularly. Owing to the pain, the investigation was terminated in 2 patients.

Vasovagal attacks. Three patients developed bradycardia and hypotension without pain when the catheter was in the left ventricle. One instance was in connection with ventricular ectopic beats. The patients recovered after a few minutes.

Intramural deposition of contrast medium. This occurred during left ventricular angiography on 7 occasions. One patient with tamponade is described under the case reports. Most of the other 6 patients developed extrasystole during the angiocardiography but they were free from symptoms. In one case where a considerable amount of contrast medium was deposited in the myocardium SGOT was elevated and ECG showed ST-T changes which were not typical for myocardial infarction. There were no sequelae.

Intramural contrast injection occurred twice during left atrial angiography, followed in one case by precordial pain but no untoward sequelae. In the other case the contrast medium had extravasated into the atrial septum but did not cause any symptoms.

Tamponade. This complication occurred in 6 cases.

PATIENT 1 (1963). G. N. was a 54-year-old man with valvular aortic stenosis in NYHA function Class III-IV. The heart volume was 460 ml. per square meter. After one TS puncture a free left atrial (LA) pressure curve was obtained. The hemodynamic observations at rest and exercise were registered. During left ventricular (LV) angiocardiography there were repeated ventricular premature beats and hypotension, accompanied by severe chest pain. Contrast deposition was seen in the myocardium, but not in the pericardium. At pericardiocentesis 300 ml. of blood was withdrawn, with rapid improvement. Another puncture had to be done some minutes later yielding 200 ml. of blood. There were no sequelae.

PATIENT 2 (1963). H. L. was a 29-year-old woman with valvular aortic stenosis, in function Class III. The heart size was 450 ml. per square meter. After repeated (6 to 7) punctures a free LV pressure curve was obtained. There was, however, persistent substernal distress. After 20 to 30 minutes hypotension occurred rather suddenly. Several pericardial punctures yielded a total of 350 ml. of blood. There was only moderate improvement and emergency thoracotomy had to be done in the heart laboratory. Blood under pressure was found in the pericardium but no perforation was found. There was an uneventful recovery. On heart surgery 6 years later there were thick pericardial adhesions but no functional constriction.

PATIENT 3 (1965). K. H. was a 48-year-old woman with combined mitral valve disease, in function Class III-IV and with a heart volume of 720 ml. per square meter. At the second TS puncture the pressure curve was atypical but the position indicated that the needle had entered LA. When the catheter was advanced over the needle an aortic pressure curve appeared. The needle and catheter was withdrawn. The patient immediately had severe chest pain with hypotension, bradycardia, and syncope. Fifty-five ml. of blood was withdrawn from the pericardium with rapid improvement. For a week there were epigastric pains but no late sequelae.

PATIENT 4 (1965). I. S. was a 31-year-old woman with combined aortic and mitral valve disease, in function Class II and with a heart size of 360 ml. per square meter. After one puncture LA and LV were reached without difficulties. During work test, approximately 30 min. after the puncture, she complained of chest pain. There was hypotension and bradycardia, followed by syncope. A vasovagal reaction was first suspected and she was given atropine and metaraminol, with some transitory effect. At pericardiocentesis, only 15 ml. of blood was found, but there was immediate improvement and no late symptoms.

PATIENT 5 (1965). G. S. was a 19-year-old woman with muscular subaortic stenosis, in function Class II and with a heart volume of 380 ml. per square meter. It was difficult to catheterize the left ventricle. After the third TS puncture the LA pressure curve was initially normal but became atypical. In order to localize the tip 10 ml. of 60 per cent Urografin was injected and was found to be deposited in the pericardium. The patient immediately complained of chest pain and became hypotensive with bradycardia. She was first given metaraminol and oxygen, and the systolic pressure rose from 46 to 100 mm. Hg. There were persistent pains and increasing venous pressure. At pericardiocentesis 85 ml. of blood was withdrawn, with rapid improvement. On heart surgery 3 months later there were no signs of any pericardial abnormalities.

PATIENT 6 (1966). This patient was a 42-year-old man with combined aortic valvular disease, in function Class II, heart volume 670 ml. per square meter. After one puncture LA and LV were easily reached and pressures measured. After a few minutes, with the catheter tip in LV the patient complained of chest pain and there was moderate hypotension and bradycardia. Atropine, oxygen, and nitroglycerine were given with rapid improvement in blood pressure and chest pains. This was repeated some times, but as the symptoms recurred and the venous pressure began to rise, pericardiocentesis was performed. Twenty-six ml. of blood was withdrawn and the patient became symptom-free. During the following hours the pericardium had to be punctured again and eventually thoracotomy was performed. A small perforation was found in the LA appendage which was sutured. The recovery was uneventful and he was operated on 7 months later.

Meticulous technique and personal acquaintance

Table IV. Complications related to TS left heart catheterization including selective angiocardiography

Complications	*Before angiography*	*During angiography*		*Total number*
		LV	*LA*	
Serious				
Cardiac perforation with tamponade	5	1		6
Cerebral embolus with sequelae	1		1	2
Minor				
Slight cerebral embolus	1		2	3
Arrhythmia	10	15	2	27
Chest pain	8			8
Vasovagal attacks	3			3
Intramural contrast injection		6	2	8
Perforation of the iliac veins	3			3
Perforation of the catheter	3			3
Breakage of the needle tip	2			2
Total number of complications	36	22	7	65
Total number of investigations	454	71	326	454

A month later the visual function was normalized.

In 3 further cases there were signs and symptoms of cerebral embolus during the course of the TS procedure but only of short duration (5 to 30 minutes). Two patients complained of paresthesia in the face one during 30 minutes after withdrawal of the catheter to the inferior vena cava, the other during 5 minutes after injection of a small test dose of contrast material. In this latter case a fibrin clot was formed at the tip of the catheter. A third patient had diplopia during 15 minutes after contrast injection into the left atrium.

Arrhythmia. Atrial fibrillation was precipitated in 7 patients during manipulation of the catheter in the right atrium before septal puncture or after recoil of the catheter from the left to the right atrium. In 5 patients the arrhythmia ceased quickly, in 3 cases spontaneously and in 2 cases after digitalization. In 2 patients atrial fibrillation lasted one day.

Atrial flutter occurred in 2 patients during the manipulation of the catheter in the right atrium. In one case the flutter was converted first after a single DC shock one day after the catheterization and in the other the arrhythmia reverted spontaneously.

Supraventricular tachycardia with block started in one patient during manipulation of the catheter in the left atrium in attempts to reach the left ventricle. It disappeared without specific treatment.

During injection of contrast medium into the left ventricle it was usual with ventricular ectopic beats. In at least 15 cases they were frequent but never released ventricular tachycardia.

During angiography from the left atrium only 2 patients developed arrhythmia. One patient had a supraventricular tachycardia which lasted only one minute. In the other patient a short period of asystole (4 seconds) occurred when the catheter recoiled back to the right atrium during the injection.

Chest pain. Eight patients complained of precordial pain during the transseptal procedure, 4 in direct connection with the puncture of the interatrial septum, 2 when the catheter was positioned in the left ventricle, and one during manipulation of the catheter in the left atrium into the pulmonary veins. In the eighth patient the pain appeared during left ventricular angiocardiography and was followed by elevation of sedimentation rate and serum glutamic oxalacetic transaminase (SGOT) but without ECG changes indicating acute myocardial infarction. This patient became symptom free in two or three days.

Precordial palpation

John F. Stapleton
Bertron M. Groves
Washington, D. C.

> The earlier clinicians, not having elaborate apparatus and complicated laboratory methods at their disposal, attempted to find signs of diagnostic value by careful observation at the bedside with the simplest clinical devices. Today these old clinical methods of examination cannot be renounced. Indeed, special attention should be given to them. A large majority of physicians are not in a position to use elaborate apparatus or complicated laboratory methods at the bedside. Furthermore, careful clinical observations—as may be demonstrated in the case of pulsatory phenomena—give important clues in diagnosis, clues such as can be brought to light by no other methods of examination, regardless of how elaborate. Following the example of the old clinicians in my studies of diagnostically important pulsations of the wall of the chest I have made use of the simplest method, namely careful inspection and palpation of the thoracic wall. In order that this method may lead to reliable results, it is indispensable that one learn it at the bedside and practice it intelligently.
>
> Wilhelm Dressler, 1937[1]

Old manuscripts reveal palpation to be an ancient technique—perhaps a mainstay of physical examination during the middle ages (Fig. 1). Today feeling the chest wall seems a crude form of investigation when compared to the sophisticated technology available. Nonetheless, painstaking examination of chest wall movement can yield valuable information quickly, easily, and safely.

Improved recording systems have promoted more precise analysis of precordial motion by permitting correlation with other biological curves such as the electrocardiogram (ECG), phonocardiogram, and intracardiac pressure pulses. Better understanding of these movements has led to more widespread use. Whereas a decade ago physical examiners usually recorded only the point of maximum impulse (PMI), today such expressions as "parasternal lift" and "late systolic bulge" are common.

Fig. 2 depicts various methods of recording precordial motion as assembled by Dimond and associates.[2] This presentation will illustrate movements with kinetocardiography. This recording system designed by Eddleman and associates[3,4] employs a flexible metal bellows probe which is held to the chest by externally supported clamps. As the chest wall moves the probe, variations of air pressure within the bellows are transmitted via a transducer to a graphic recorder. The probe itself is a slender metal rod having a 7 mm. wide tip. Although not as popular as apex cardiography, kinetocardiography offers several advantages related to external fixation of its pickup device: (1) movements can be recorded from any part of the precordium, (2) the system can register motion whether subtle or gross, diffuse or local, retractile or expansile, and (3) the tracings are displace-

From the Department of Medicine, Georgetown University Hospital, Washington, D. C.
Reprint requests to: Dr. John F. Stapleton, Department of Medicine, Georgetown University Hospital, 3800 Reservoir Rd., N.W., Washington, D. C. 20007.

29 Kahler R L and Braunwald E. The contribution of modern hemodynamic techniques to the diagnosis of acquired heart disease Med. Clin. N Amer 46:1519 1962.
30 Lindeneg O Nielsen M H and Hansen A T Transseptal left heart catheterization with puncture of the interatrial septum Acta Med. Scand 175:57 1964
31 Bette, L. and Harbauer G Transseptal catheterizations of the left heart Jap. Heart J 5:301 1964
32 McIntosh H D Sleeper J C. Thompson H K. and Whalen R. E. Simplification of left heart catheterization percutaneous technique for catheter insertions, J.A.M.A. 177:600 1961
33 Peckham G B Chrysohou A. Aldridge H E. and Wigle, E. D Combined percutaneous retrograde aortic and transseptal left heart catheterization Brit. Heart J 26:460 1964
34 Verel, D Catheterization of the left atrium by Ross needle and Seldinger wire techniques, Brit. Heart J 29:380 1967
35 Adrouny Z. A., Sutherland D W Griswold H E and Ritzmann L W Complications with *transseptal left heart catheterization*, AMER. HEART J 65:327 1963
36. Braunwald E. and Swan H. J C Cooperative study on cardiac catheterization Circulation 37:3 1968. Suppl.
37 Arvidsson, H Angiocardiographic determination of left ventricular volume, Acta Radiol 56:321 1961
38 Nixon P G F and Ikram H Left heart catheterization with special reference to the transseptal method Brit Heart J 28:835 1966
39 Braunwald E. Brockenbrough E. C Talbert J L. Folse J R. and Rockoff S D Selective left heart angiocardiography by the transseptal route, Amer J Med 33:213 1962
40. Demiroglu C. Ozcan, R. Tuzlaci, M Danopulos, D Öztürk M and Garan, R Ursachen der Komplikationen bei transeptaler Angiokardiographie Z. Kreislaufforsch 55:897 1966
41 Beuren, A J and Apitz, J Left ventricular angiocardiography by transseptal puncture of the left atrium Circulation 28:209 1963
42 Nadimi M Anagnostopoulos, L. D and Frank, M J Cardiac tamponade after transmyocardial extravasation of contrast material AMER. HEART J 2:369 1966.
43 Ross, J Considerations regarding the technique for transseptal left heart catheterization Circulation 31:391 1966.
44 Brockenbrough E. C. Braunwald E and Ross, J Transseptal left heart catheterization Circulation 25:15 1962
45 Larker J O West R O and Fay J E. The Brockenbrough transseptal catheterization, Circulation 30:743 1964
46. Kosowsky W A., and Bleifer S. B Fatal cerebral embolism complicating transseptal left heart catheterization, Circulation 32:811 1965
47 Pinkerson, A. L. Kelser G. A and Adkins, P C. Mural thrombus in the left atrium secondary to transseptal catheterization of the left side of the heart, New Eng J Med 268:367 1963
48. *Nixon P G F The transseptal approach to the* left atrium in mitral regurgitation, Thorax 15:225 1960.
49 Bulloch R T., Murphy M L. and Bates J H Criteria for avoiding transseptal cardiac catheterization in the diagnosis of left atrial myxoma, Southern Med. J 59:1313 1966.
50 Duke M and Fife J Massive retroperitoneal hemorrhage Amer J Cardiol 11:823 1963
51 Sumano A. and Carleton R. A. Trans-septal catheterization of the left atrium New Eng J Med. 270:897 1964
52. Cournand A. Motley H L. Himmelstein A Dresdale, D., and Baldwin J Recording of blood pressure from the left auricle and the pulmonary veins in human subjects with inter auricular septal defect, Amer J Physiol 150:267 1947
53 Aldridge H E. Transseptal left heart catheterization without needle puncture of the inter atrial septum Amer J Cardiol. 13:239 1964
54 Bloomfield, D A., and Sinclair-Smith B C. The limbic ledge A landmark for transseptal left heart catheterization, Circulation 31:103 1965
55 Bette, L., Blase H Doenecke P Ebeling, J Heinz, H Hoffmann K. Kobayashi, T and Schleffer H Blunt transseptal catheterization of the left heart, German Med Monthly 11:396, 1966
56. Russell R O Carroll J F *and Hood W G* Cardiac tamponade, Amer J Cardiol 13:558 1964
57 Christiansen I and Wennevold A. Complications in 1 056 investigations of the left side of the heart, AMER. HEART J 71:601 1966.

parasternal region which is not ordinarily felt in older children or adults. One can often see and feel systolic retraction in the lower left parasternal region in young slender people or in patients with hyperactive cardiac motion. Atrial and other movements are usually palpated only in disease states.

Numerous terms descriptive of precordial movements, have entered the language of physical diagnosis in recent years words such as heave lift, and thrust all refer to outward movement. Although thrust implies a brisker movement than heave or "lift there is much overlap in the use of these words. Eddleman and Harrison introduced the word "bulge" to describe the abnormal systolic movement of myocardial infarction. The term shock refers to the brief palpable impact of a loud heart sound Precordial pulsation impulse" vibration, or "pulse refer to any type of chest wall movement.

The technique of palpation

Palpation is not difficult, requiring only time and care. A few moments of concentration can convert a cursory examination into a meaningful one.

Careful inspection should precede palpation some movements are seen better than felt others are felt better than seen. Gross movements are readily perceived subtle pulsations easily escape notice. It is better to look across the chest surface from a tangential visual angle than to look directly down from above Shining a light across the apical region so as to create shadows, may unmask a fine pulse, unseen in full direct light. Sometimes parasternal motion is best perceived by looking up the chest from the foot of a bed (a good position from which to judge chest symmetry)

Having inspected the examiner prepares to palpate he should stand at the patient's right (also the best location for auscultation) and extend his right hand at a comfortable waist-high level. Stooping to a low bed or hanging over a side rail can lessen one's acuity hyperextending the hand to compensate for bad position should be avoided

When palpating the examiner feels the precordial sites in the same sequence as when ausculting He begins at the apex, palpating any movement seen on inspection. He should feel for a few moments, since a brief warm-up period seems to improve perception of faint impulses. This process of adjustment has been likened to the tuning in" period necessary to auscult faint heart murmurs. He then shifts his hand sequentially to the left parasternal region the sternum itself the right parasternal area, the epigastrium and then to the cardiac base

Although this presentation will cover only precordial movements, it is important for physicians to palpate over the upper sternum the sternoclavicular joints and the supraclavicular fossae since aneurysms may present abnormal pulsations in these areas.

When feeling for localized movement, as at the apex, it is helpful to use the distal palmar surface of apposed fingers. When feeling for diffuse movement as over the left parasternal region one can use either the distal surface or the heel of the palm Of course the physician may modify this routine according to his own experience.

The patient should be supine for the basic palpation procedure. Although movements may be well felt with the subject sitting or turned on the left side normal values are not well established for postures other than supine. Angiocardiography shows the heart to shift against the chest wall in the left lateral decubitus position causing sustained systolic outward chest wall movement. Since the duration of systolic impulse is a sensitive index of abnormality we prefer to study patients in the supine posture wherein the normal duration of outward thrust is brief well known, and fairly constant. In the clinical setting there is additional value to palpation in the left lateral recumbent position as will be discussed later Fig 3 illustrates the striking exaggeration of duration and amplitude which occurs when the apical impulse is palpated with the patient turned on his left side

The upright posture may obscure abnormal leftward shift of cardiac pulsation by allowing an enlarged heart to assume a more vertical position A tall slender patient is especially liable to shift his left



Fig 1 Palpation in the fourteenth century The illustration from a 1345 manuscript shows a physician palpating his patient (Reproduced courtesy of Musée Condé Chantilly France and the Journal of the American Medical Association.)

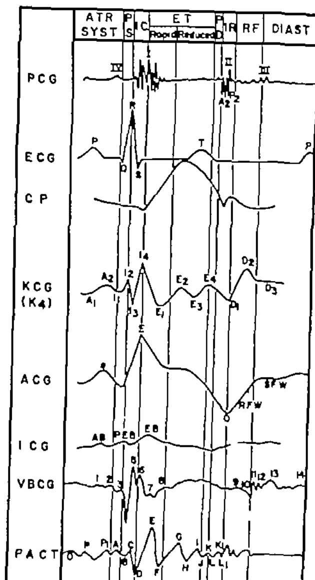


Fig 2 Comparison of precordial movement tracing obtained by different recording techniques. *PCG* = Phonocardiogram *ECG* = electrocardiogram *CP* = carotid pulse *KCG* = kinetocardiogram *ACG* = apexcardiogram *ICG* = impulse cardiogram *VBCG* = vibrocardiogram *PACT* = precordial accelerogram (From Dimond Duenas, and Benchimol Apex cardiography Amer. Heart J 72:124 1966)

ment curves which depict what is palpated

Kinetocardiographic leads are labelled like electrocardiographic leads, the designation K substituting for the electrocardiographic V Thus K_2 indicates placement of the probe in the fourth left interspace at the sternal edge while K_4 represents the usual location of the apical impulse The baseline has been established as a horizontal line drawn through the movement tracing at a point 0 04 sec after the onset of the electrocardiographic QRS Outward movements cause upward deflections while inward movements cause downward deflections

Although the kinetocardiogram (KCG) reveals numerous deflections, only the major ones have palpatory significance These are (1) a brisk upward deflection (outward movement) with beginning systole followed by (2) a swift downward deflection (inward movement) during systolic ejection which (3) returns to the baseline during diastolic filling and (4) a brief upward deflection then occurs during atrial systole The initial brief outward systolic movement is usually palpable at the apex where it comprises the apical impulse or point of maximum impulse. Infants may present a palpable brief early systolic thrust over the sternum and left lower

parasternal region which is not ordinarily felt in older children or adults. One can often see and feel systolic retraction in the lower left parasternal region in young slender people or in patients with hyperactive cardiac motion. Atrial and other movements are usually palpated only in disease states.

Numerous terms, descriptive of precordial movements, have entered the language of physical diagnosis in recent years words such as "heave," "lift," and "thrust" all refer to outward movement. Although "thrust" implies a brisker movement than "heave" or "lift," there is much overlap in the use of these words. Eddleman and Harrison introduced the word "bulge" to describe the abnormal systolic movement of myocardial infarction. The term "shock" refers to the brief palpable impact of a loud heart sound. Precordial "pulsation," "impulse," "vibration" or "pulse" refer to any type of chest wall movement.

The technique of palpation

Palpation is not difficult, requiring only time and care. A few moments of concentration can convert a cursory examination into a meaningful one.

Careful inspection should precede palpation; some movements are seen better than felt, others are felt better than seen. Gross movements are readily perceived; subtle pulsations easily escape notice. It is better to look across the chest surface from a tangential visual angle than to look directly down from above. Shining a light across the apical region so as to create shadows may unmask a fine pulse unseen in full direct light. Sometimes parasternal motion is best perceived by looking up the chest from the foot of a bed (a good position from which to judge chest symmetry).

Having inspected, the examiner prepares to palpate. He should stand at the patient's right (also the best location for auscultation) and extend his right hand at a comfortable waist high level. Stooping to a low bed or hanging over a side rail can lessen one's acuity; hyperextending the hand to compensate for bad position should be avoided.

When palpating, the examiner feels the precordial sites in the same sequence as when auscultating. He begins at the apex palpating any movement seen on inspection. He should feel for a few moments since a brief warm up period seems to improve perception of faint impulses. This process of adjustment has been likened to the "tuning in" period necessary to auscultate faint heart murmurs. He then shifts his hand sequentially to the left parasternal region, the sternum itself, the right parasternal area, the epigastrium, and then to the cardiac base.

Although this presentation will cover only precordial movements, it is important for physicians to palpate over the upper sternum, the sternoclavicular joints, and the supraclavicular fossae, since aneurysms may present abnormal pulsations in these areas.

When feeling for localized movement, as at the apex, it is helpful to use the distal palmar surface of apposed fingers. When feeling for diffuse movement, as over the left parasternal region, one can use either the distal surface or the heel of the palm. Of course, the physician may modify this routine according to his own experience.

The patient should be supine for the basic palpation procedure. Although movements may be well felt with the subject sitting or turned on the left side, normal values are not well established for postures other than supine. Angiocardiography shows the heart to shift against the chest wall in the left lateral decubitus position causing sustained systolic outward chest wall movement. Since the duration of systolic impulse is a sensitive index of abnormality, we prefer to study patients in the supine posture, wherein the normal duration of outward thrust is brief, well known and fairly constant. In the clinical setting there is additional value to palpation in the left lateral recumbent position, as will be discussed later. Fig. 3 illustrates the striking exaggeration of duration and amplitude which occurs when the apical impulse is palpated with the patient turned on his left side.

The upright posture may obscure abnormal leftward shift of cardiac pulsation by allowing an enlarged heart to assume a more vertical position. A tall slender patient is especially liable to shift his left

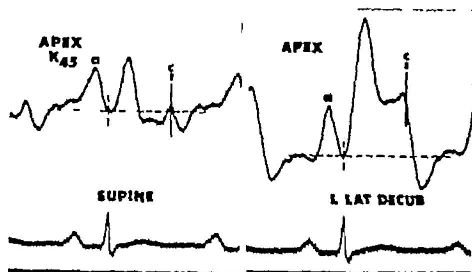


Fig. 3. Atrial and early systolic impulses caused palpable double movement in a 48-year-old man with myocardiopathy which commenced with typical acute idiopathic pericarditis four years before above tracing. Note that the early systolic thrust heightens and becomes holosystolic when the patient turns on his left side. *CI* = Carotid incisura. *a* = atrial movement.

precordial movement medially by sitting or standing. Positional change of this kind explains the occasional patient whose recumbent PMI is abnormally leftward but whose upright inspiratory chest x-ray suggests normal heart size.

Simultaneous auscultation for timing is fundamental to accurate palpation. It is seldom possible to clearly identify systole and diastole by palpation alone. Distinction between presystolic, early systolic, late systolic, and diastolic movements can have important clinical meaning. Many interpretive errors have resulted from improper timing of precordial movements.

Apical impulse

With beginning ventricular contraction there occurs a brisk localized thrust at the cardiac apex known as the apical impulse or point of maximum impulse (PMI). The term PMI is sometimes inaccurate since more vigorous impulses may occur elsewhere on the chest wall in certain disease states. However, the PMI has so long connoted the left ventricular apical impulse and is so familiar to physicians as to require mention in this presentation. Apical impulse is a preferable expression.

When recorded by kinetocardiography, this movement is seen to begin about 0.08 sec. after the onset of QRS and to precede the carotid upstroke by 0.01 to 0.02 sec. It occurs, therefore, at the very onset of left ventricular ejection and probably represents recoil movement which develops as left ventricular output meets aortic resistance.[6]

It is normally a very brief movement lasting about 0.04 sec. As ejection continues, left ventricular volume declines and the chest wall promptly retracts; this inward movement is sustained throughout systole (Fig. 4). Angiocardiography has disclosed the actual cardiac impingement site to be the lower anteroseptal surface just above the anatomical cardiac apex.[7]

The apical impulse is normally within the left midclavicular line in the fifth intercostal space. Its zone of perceptibility seldom exceeds a square inch; its action is usually gentle. Most children and young adults have palpable apical pulsations. The apex movement declines with advancing years although many persons of middle or elderly age continue to have detectable impulses if carefully sought. Obesity, emphysema, or heavy chest musculature may obscure the apical impulse; slenderness serves to accentuate it.

At times the vibration of an unusually loud first heart sound causes a palpable impact which dominates tactile perception at the apex. This often occurs in mitral stenosis and in high cardiac output states.

Apical movements can deviate from normal as to location, amplitude, duration, and area. The examiner must assess and record

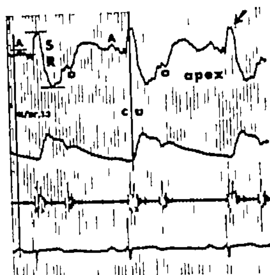


Fig. 4 The normal apical impulse (arrow) is brief early systolic thrust followed by more pronounced systolic retraction which persists throughout ejection. *A* = Atrial outward movement, *SR* = systolic retraction *a/sr* = ratio of trial outward movement to systolic retraction *cu* = carotid upstroke = onset of diastolic filling

all these characteristics, for a given impulse may have only one abnormal feature.

Displacement of the apical impulse is one of medicine s most valuable clinical signs. Unless the heart is shifted by an extra cardiac process (such as pneumothorax) or musculoskeletal deform ty (as in pectus excavatum) leftward displacement of the supine apex pulsation means heart disease.

Painstaking search for the apical pulsa tion may be rewarding Sometimes when the impulse is not readily perceived it is useful to palpate with the patient turned onto his left side an imperceptible supine movement may become palpable after turning The examiner may then discover the supine apical mpulse to be just medial to the lateral decubital pulsation. By look ing and feeling carefully he may appreciate a faint impulse previously overlooked in the supine position. Occasionally exercise or inhalation of amyl nitrite may render palpable or visible a previously undetect able pulsation particularly if the patient turns on his left side

A common interpretive problem involves the overactive impulse. Numerous condi tions increase the magn tude and area of pulsation without affecting its duration or location. These cond tions may or may not represent intrinsic heart disease. Hyper thyroidism or severe anemia commonly exaggerate the cardiac impulse (Fig 5) Occasionally the vigorous cardiac action of healthy young adults causes a forceful apical pulsation especially when the chest is slender and the individual anxious.

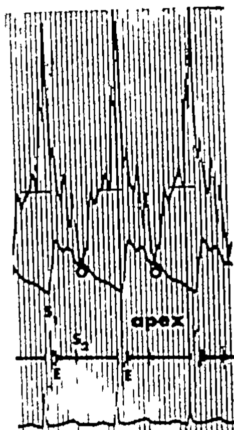


Fig. 5 Overactive apical impulse of thyrotoxicosis (top tracing) Note rapid return to baseline of greatly heightened initial outward thrust. Normal contour except for increased amplitude. N evidence of heart disease. S = First heart sound S = second heart sound; E = ejection sound; = onset of diastolic filling

It is often difficult to determine when increased magnitude of an impulse exceeds normal limits. The kinetocardiogram may be helpful in such cases. Usually the upward initial deflection in early systole is smaller than the systolic retraction which immedi ately follows. Hence the ratio of initial systolic outward movement to initial sys tolic inward movement is normally less than 1.0 The healthy young person with

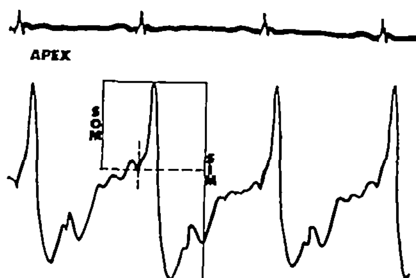


Fig 6 Hyperactive apical impulse in a 25 year-old man with acute idiopathic pericarditis Myocarditis with cardiac dilatation suspected because of persisting vigorous, though normally located, apical impulse. Apex kinetocardiogram disclosed brisk, early systolic outward movement (*SOM*) followed by a much larger systolic inward movement (*SIM*) The ratio of outward to inward movement remains well below 1 0 the tracing contour is normal The apical impulse therefore is normal though hyperkinetic. (Fig retouched.)

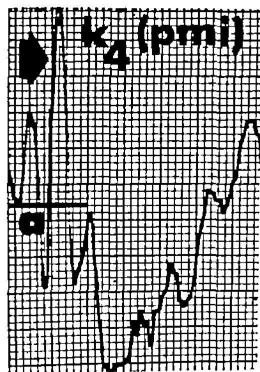


Fig 7 Overactive apical impulse of mild aortic regurgitation. Impulse neither displaced nor abnormally sustained. This curve represents earliest movement abnormality of aortic regurgitation *a* = Atrial movement.

a vigorous apical thrust exaggerates out

remains unchanged or declines. Therefore the ratio of outward to inward movement changes and often exceeds 1 0

This problem was illustrated by a 25 year-old man with acute idiopathic pericarditis Although his findings were promptly controlled by steroids an excessively forceful apical impulse raised concern over possible persisting myocardiopathy Fig 6 displays his apex kinetocardiogram which disclosed the heightened initial outward thrust to be followed by deep retraction thus his KCG retained a normal configuration and did not indicate significant myocardial disease

Apical impulse abnormality relates most commonly to left ventricular hypertrophy and or dilatation Palpable alteration of the apex movement occasionally precedes x ray or ECG evidence of left ventricular hypertrophy Distortion of the apex kinetocardiogram frequently antedates other evidence of left ventricular disease.[9]

Volume overloading (as in aortic regurgitation) and pressure overloading (as in aortic stenosis) have different effects upon the apical impulse Mild volume overloading causes only an overactive impulse indistinguishable from those caused by extra

pulsation. Only in severe disease does the impulse become significantly prolonged

Pressure overloading increases the duration of the apical systolic outward movement. The apical impulse does not shift leftward until later in the course than with comparably severe volume overloading. The apical thrust tends to be less overactive. At times, the sustained left ventricular impulse of aortic stenosis may extend to the sternal border and even to the subxyphoid region.

Location of the apical impulse in aortic valve disease has important clinical implications. Displacement to the left in pure aortic stenosis usually denotes advanced disease. Displacement to the left in pure aortic regurgitation is consistent with asymptomatic state and good cardiac function for years. Displacement to the left in mixed aortic valve disease favors predominant regurgitation unless congestive heart failure has supervened.

It is possible for the skillful physician, who times his palpatory findings carefully and correlates them with the remaining clinical data, to draw important inferences regarding volume and pressure overloading. Certitude is difficult to achieve, however and the examiner must remember that considerable overlap exists between these movement patterns.

In the late stage of aortic valve disease of any type, the apical impulse becomes a prolonged, systolic outward lift—extending from the first to second heart sound. Palpable distinctions between volume and pressure overloading are lost at this stage.

The KCG can often provide helpful documentation in these cases. It is difficult to appreciate minor changes in duration by palpation alone however the measurement can easily be made on an apex kinetocardiogram which can confirm the significance of borderline impulses. Eddleman has shown the normal duration of the initial outward movement to average 0.045 sec. ± 0.02 sec. Measurements exceeding 0.09 sec. generally indicate an underlying abnormality. Such kinetocardiographic measurements require careful recording techniques. One should consult the publications of Eddleman and associates[1, 15] for more details.

In addition to volume and pressure overloading conditions primary myocardial diseases also affect the apical impulse causing displacement and increased amplitude area, and duration. The movement steadily spreads lengthens, and heightens as the disease advances. Palpating and recording apical pulsations help to assess myocardial status and afford the physician an excellent followup parameter. An occasional patient with improving myocardiopathy regains normal electrocardiographic and x-ray configuration but retains an abnormal apical impulse. In such cases, persisting displacement or prolongation of the apex movement may alert the physician to the need for continuing surveillance and restriction of physical effort.

A sustained systolic impulse appears to indicate more seriously disturbed myocardial function than does the heightened PMI. Sutton and associates have recently demonstrated that sustained outward systolic movement correlates with reduced myocardial contractility whereas increased amplitude often occurs with normal myocardial function. Their study supports the clinical observation that the heart tolerates volume overloads better than pressure overloads.

The pathophysiology of abnormal left ventricular pulsation is not wholly clear. Deliyannis and associates[7] ascribe the prolonged apical impulse to hypertrophy of the middle circular myocardial layer whose increased bulk counteracts the normal apical retraction caused by contraction of internal and external spiral muscle fasciculi.

Rarely does the apical impulse exhibit only retraction during systole. Tricuspid regurgitation and constrictive pericarditis are the conditions most commonly responsible for this inversion of the usual apical movement.[12]

Lower left parasternal systolic movement

The right ventricle underlies the anterior precordium adjacent to the lower sternal edge. Although KCG's frequently disclose a small vertical outward thrust in this area this is not usually felt beyond infancy. However a diffuse inward movement during systole is often visible and palpable. One can appreciate this retraction by resting the unheld stethoscope at K_1 or K_2 and

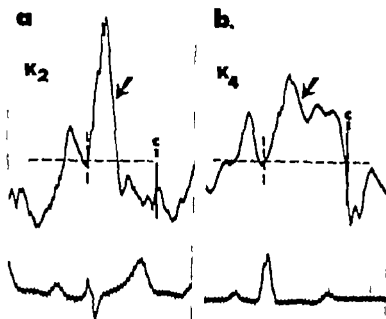


Fig 8 a and b a Lower left parasternal movement (K_2) of 12 year-old boy with atrial septal defect (1 7/1.0 left to-right shunt) and normal pulmonary artery pressure. Note forceful, brief early systolic thrust with prompt retraction (arrow) well below the baseline ci = Carotid incisura b Apical impulse (K_4) of right ventricular origin obtained from 26-year-old man with atrial septal defect (1.8/1 0 left to-right shunt) and markedly elevated pulmonary artery pressure (75/30 mean 43 mm. Hg) Note initial outward movement with minimal retraction (arrow) followed by outward movement sustained to the end of systole The total systolic impulse remains well above the basel ne

observing its inward systolic movement while auscultıng

Right ventricular hypertrophy or dilatation increases the initial parasternal thrust Like the left ventricular apical impulse the abnormal right ventricular impulse becomes greater and longer Volume overloading tends to exaggerate magnitude (Fig 8 a) while pressure overloading tends to exaggerate duration (Figs. 8 b and 9) Eddleman has used this distinction to differentiate kinetocardiographically the right ventricular movement of atrial septal defect from that of mitral stenosis. He found that atrial defect causes an early brief exaggeration of systolic outward thrust whereas mitral stenosis causes a more sustained systolic lift featuring less systolic retraction [13] While kinetocardiographic measurements can reliably separate these two conditions, carefully timed palpation can also suggest different movement characteristics of right ventricular pressure and volume overloading though less accurately than do recordings [14]

Right ventricular movement may also cause a subxyphoid pulsation Although this impulse often accompanies lower left parasternal movement a right ventricular thrust is sometimes felt best just beneath the xyphoid this is especially important in patients with pulmonary emphysema who may have no precordial pulsations. The physician s hand should probe deeply in the epigastrium and upward beneath the xyphoid and left costal margin to appreciate this impulse The examiner must distinguish the superiorly located diaphragmatic right ventricular impulse from the more deeply located abdominal aortic pulsation

Extension of right ventricular outward movement to the second heart sound usually indicates either pulmonary hypertension or left atrial enlargement. Eddleman has called attention to the early systolic thrust of pulmonic stenosis which falls off in mid systole and does not persist to the second sound presumably because of pulmonary hypotension [13] The impulse of atrial septal defect extends into late systole only when pulmonary hypertension coexists (Fig 8) On the other hand patients with mitral regurgitation may exhibit a sustained systolic parasternal lift when the



Fig. 8c. Right heart catheter positioning confirmed right ventricular occupancy of cardiac apex (cf -ray)

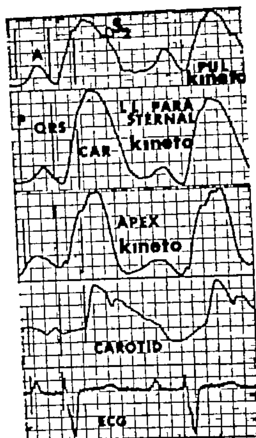


Fig 9 Diffuse outward systolic lift of 17-year-old woman with severe primary pulmonary hypertension. Pulmonic impulse has contour identical to that of lower precordial movements. *car* = Carotid upstroke *A* = trial movement. (From Stapleton nd Lindberg: Palpation of the precordium, GP 34 107 1966.)

left atrium is big even though pulmonary artery pressure may be normal or slightly elevated (Fig 10)

The enlarged left atrium of mitral stenosis tends to push the heart forward against the sternum, exaggerating the sternal component of the right ventricular movement. For this reason, mitral stenosis causes a more medial maximum thrust as compared to other causes of right ventricular hypertrophy When severe pulmonary hypertension complicates mitral stenosis, the maximum systolic thrust may occur in the lower right parasternal region.[12] In contrast, atrial septal defect causes a systolic thrust maximum at K or K_3. Pulmonic stenosis causes an impulse which is even more lateral often peaking at K_4.[13]

Besides pressure and volume loading conditions, primary myocardial diseases also cause abnormal right ventricular pulsations, leading to heightened and lengthened lower left parasternal systolic movements. Often the abnormal apical impulse of left ventricular disease is also present. Rarely is the myocardiopathy predominantly right ventricular the precordial impulse in such patients is similar to that of pulmonary hypertension, the apex pulsation being normal or impalpable.

An apparent left ventricular apical impulse in right ventricular disorders often turns out to be the peripheral component of a diffuse precordial movement which extends from the apex to the sternum (Fig 8 *b*) In such conditions, the enlarged right ventricle constitutes the entire anterolateral surface of the heart. This circumstance will be discussed further in a later section

Extracardiac conditions which displace the heart anteriorly may also account for increased and prolonged left parasternal systolic movement. Fig 11 presents the impulse tracing of a 51 year-old man with eventration of the left diaphragm whose

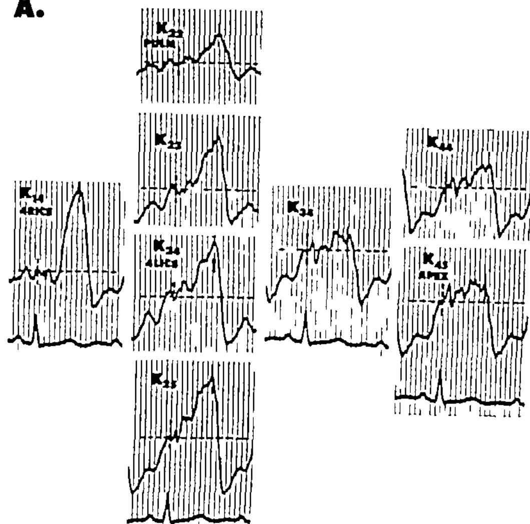


Fig 10A The widely distributed late systolic lift of a 51 year-old woman with moderately severe mitral regurgitation with mild elevation of pulmonary artery pressure (40/15 mm. Hg) Note that late systolic movement, palpable all over the precordium, has similar contour wherever recorded.

heart was displaced anteriorly and to the right causing an impressive left lower parasternal systolic lift thought at first to represent right ventricular hypertrophy Although he had flattened electrocardiographic T waves a midsystolic click was the only abnormal physical finding he played tennis vigorously without difficulty and had normal heart size and no history of cardiovascular or pulmonary illness.

Simultaneous auscultation and palpation of the lower left parasternal region will prevent serious timing errors wherein the rapid return to the baseline of a vigorous systolic retraction might be mistaken for an abnormal systolic thrust. Fig 12 illustrates this phenomenon in a young woman with hyperkinetic heart action Constrictive pericarditis may also cause systolic retraction and a brisk palpable diastolic return the latter coinciding with the early diastolic third heart sound of pericardial constriction The diastolic thrust of constrictive pericarditis augments with inspiration and may extend across the precordium A similar process can occur in restrictive myocardiopathy (Fig 13)

Striking parasternal systolic retraction commonly occurs when marked left ventricular dilatation causes unusual prominence of the apical impulse (Fig 14) Severe aortic regurgitation can lead to the erroneous impression of biventricular enlargement Palpation of the apex and parasternal areas with two hands can reveal the asynchrony of the apex and parasternal movements Simultaneous auscultation will also clarify the nature of this movement

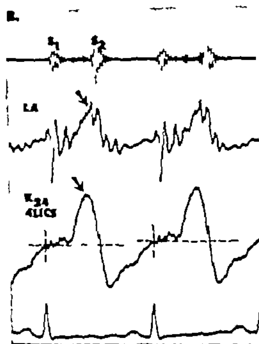


Fig *10B* Simultaneously recorded left trial (LA) pressure pulse nd lower left parasternal impulse (K_{24}) Observe similarity of intracardiac left trial \ av (arrow) and late systolic lift (arrow) Absence of exaggerated early systolic impulse correlates ith near-normal pulmonary artery pressure.

pattern. When parasternal systolic outward movement does accompany the ponderous apical impulse of severe aortic regurgitation one should seek additional explanation

Lower right anterior chest movement

Both mitral and tricuspid regurgitation may cause systolic pulsation of the lower right anterior chest occasionally extending to the right anterior axillary line. In such cases, the liver often presents similar pulsations. These impulses derive from the ventricularized pressure pulses arising from the rightwardly displaced atria of mitral or tricuspid regurgitation.

Tricuspid stenosis can give rise to presystolic movement of the right lower chest and liver This diagnosis can be inferred by noting a prominent jugular A wave associated with presystolic hepatic impulse w thout systolic right ventricular impulse The right ventricular pulsation in this condition is normal or absent, unless pulmonary hypertension coexists. Most conditions which exaggerate jugular A waves also cause the systolic thrust of right ventricular hypertrophy (with the exception of atrioventricular dissociation)

Atrial movements The normal KCG discloses small atrial deflections which are not



Fig *11* Eventration of the left diaphragm in 51-year-old man ith anterior displacement of the heart causing abnormal diffuse cardiac impulse. T flattening and systolic click (SC) may also have related to this positional anomaly although minor mitral valve defect could not be ruled out. The patient engaged in vigorous athletics ithout symptoms and had normal heart size. Above tracing recorded over mid precordium. = Extrasystole cu = carotid upstroke.

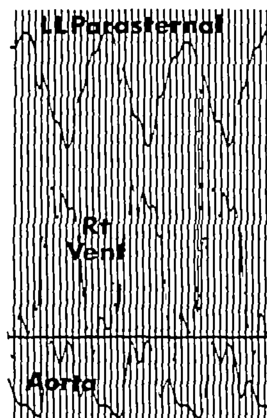


Fig 12 Vigorous systolic retraction in young woman *with high cardiac output (10 L. per minute) due to* respiratory insufficiency of far advanced pulmonary tuberculosis. Hyperdynamic diastolic thrust was mistaken for systolic lift of right ventricular hypertrophy (From Stapleton and Lindberg Palpation of the precordium, GP 34:107 1966.)

normally felt. Various disease states make such movements palpable Atrial contraction creates chest wall pulsation by causing exaggerated ventricular distention with resultant forward thrust of the ventricles.[17] Thus the term atrial impulse actually refers to a ventricular impulse caused by atrial systole Atrial movements are usually presystolic but may occur whenever atrial contraction occurs.

Conditions which increase resistance to ventricular filling augment the force of atrial systole causing exaggerated atrial thrust Resistance to ventricular filling usually means reduced myocardial compliance as found in the thick walled left ventricle of systemic hypertension or aortic stenosis. The right ventricle is similarly involved in pulmonary hypertension or pulmonic stenosis. Thus the palpable ventricular distention of atrial contraction can arise from either atrium Therefore right atrial pulsation is maximum in the lower left parasternal area and left atrial pulsation is maximum at the apex[18] (and may be felt only in the left lateral decubitus position)

Atrial movements are easily felt when solitary or when well separated from other pulsations. The interval between atrial and

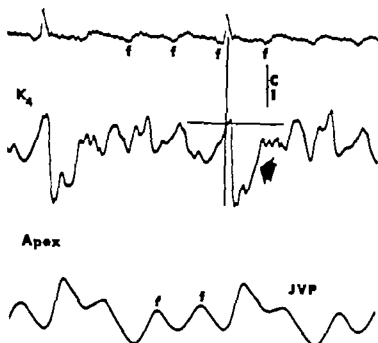


Fig. 13 Restrictive myocardiopathy in a 21 year-old woman whose clinical findings so resembled constrictive pericarditis that she underwent exploratory thoracotomy Lower left parasternal pulsation thought to be a systolic thrust. Kinetocardiogram discloses impulse to consist of brisk diastolic return to baseline (arrow) following systolic retraction. *f* = Atrial flutter waves *JVP* = jugular venous pulse *ci* = carotid incisura.

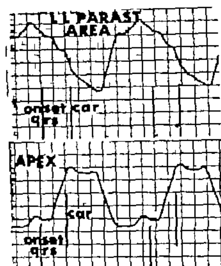


Fig. 14 Striking left parasternal systolic retraction in 72-year-old woman with marked left ventricular enlargement and complete left bundle branch block. Etiology: probable myocardiopathy Two-handed palpation revealed asynchronous rocking motion. Note late decline of systolic outward movement relative to QRS. car = Carotid upstroke. (From Stapleton and Lindberg Palpation of the precordium, GP 31 107 1966.)

ventricular impulses depends upon the P R interval. Often, therefore the atrial movement occurs so close to an early systolic ventricular movement as to be included in the latter impulse unless the physician pays careful attention to the small vibration at the onset of the larger movement. Mounsey has likened the atrial movement in this circumstance to a musical grace note.[18]

Kinetocardiograms during acute myocardial infarction regularly reveal heightened atrial deflections.[19] Sometimes atrial movement becomes palpable during the first few days after infarction, particularly when heart failure supervenes. The movement then lessens as myocardial function improves.

The most impressive atrial thrust occurs in primary myocardial disease. The movement may achieve "giant" proportions and become palpable across the precordium.[17] If mistimed the atrial impulse of myocardiopathy can simulate the systolic lift of ventricular hypertrophy [21]

When the underlying disease causes both atrial and ventricular pulsation, the examiner can often appreciate a double or bifid impulse (Fig 3) This palpatory finding should suggest one of the conditions just described. Commonly present in myocardiopathies, double movement is especially characteristic of hypertrophic subaortic stenosis as discussed below

The late systolic thrust of mitral regurgitation may blend with abnormal early systolic movement due to left and/or right ventricular hypertrophy and dilatation. Isolated outward late systolic movement, therefore, suggests an earlier stage of mitral incompetence as compared to holosystolic or bifid systolic impulse.

Advanced mitral regurgitation can also cause a palpable early diastolic rapid filling tap and when regurgitation develops abruptly as a result of chordal rupture an atrial impulse may develop The movement pattern of mitral incompetence is, therefore variable and requires timing and clinical correlation

Myocardial Infarction

Acute myocardial infarction often causes a pronounced outward systolic movement. Most commonly there occurs an early systolic thrust which is sustained to mid or late systole. Less often the impulse commences later in systole. Eddleman and Harrison[19] have employed the term "systolic bulge" to describe this movement, defining a bulge as an outward thrust lasting 0.02 sec. or more. A bulge characterizes 70 per cent of acute transmural infarcts persisting permanently in 60 per cent of the patients.[22] It is usually maximum at K_2, K_3, or K_4 but occasionally is best felt in the epigastrium. The bulge which peaks at K or K may closely simulate right ventricular hypertrophy although kinetocardiographic distinctions are usually possible. The bulge at K_4 may be indistinguishable from the impulse of left ventricular hypertrophy The palpatory findings of myocardial infarction must be correlated with other clinical findings. Bulges may occur with anterior or posterior infarction and may develop transiently during angina pectoris.

Coronary patients without bulges may have less prolonged outward systolic movements and often have increased atrial pulsations as described above. Some patients who lose their bulges as they recover nevertheless retain kinetocardiographic abnormalities.[22]

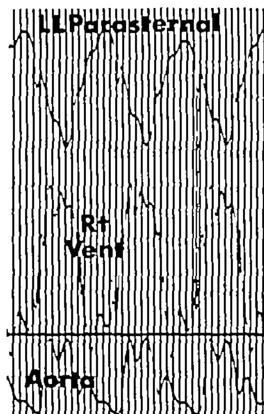


Fig. *12* Vigorous systolic retraction in young woman with high cardiac output (10 L. per minute) due to respiratory insufficiency of far advanced pulmonary tuberculosis. Hyperdynamic diastolic thrust was mistaken for systolic lift of right ventricular hypertrophy (From Stapleton and Lindberg Palpation of the precordium GP 31 107 1966.)

normally felt Various disease states make such movements palpable Atrial contraction creates chest wall pulsation by causing exaggerated ventricular distention with resultant forward thrust of the ventricles.[17] Thus the term atrial impulse actually refers to a ventricular impulse caused by atrial systole Atrial movements are usually presystolic but may occur whenever atrial contraction occurs.

Conditions which increase resistance to ventricular filling augment the force of atrial systole causing exaggerated atrial thrust Resistance to ventricular filling usually means reduced myocardial compliance as found in the thick walled left ventricle of systemic hypertension or aortic stenosis. The right ventricle is similarly involved in pulmonary hypertension or pulmonic stenosis. Thus the palpable ventricular distention of atrial contraction can arise from either atrium Therefore right atrial pulsation is maximum in the lower left parasternal area and left atrial pulsation is maximum at the apex[18] (and may be felt only *in the left lateral decubitus position)*

Atrial movements are easily felt when solitary or when well separated from other pulsations. The interval between atrial and

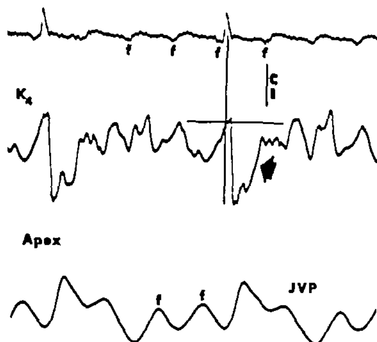


Fig. *13* Restrictive myocardiopathy in a 21 year-old woman whose clinical findings so resembled constrictive pericarditis that she underwent exploratory thoracotomy *Lower left parasternal pulsation thought to be a* systolic thrust. Kinetocardiogram discloses impulse to consist of brisk diastolic return to baseline *(arrow)* following systolic retraction. *f* = Atrial flutter waves *JVP* = Jugular venous pulse; *ci* = carotid incisura.

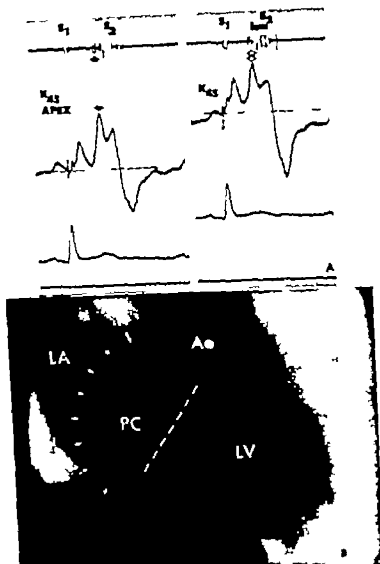


Fig. 15 *A* and *B* Apical impulse and heart sounds of 52-year-old man with prolapsing posterior mitral cusp (*PC*) with mild mitral regurgitation. Note that late systolic impulse (arrows) peaks with midsystolic click ( ) Late systolic murmur (sm) follows. X-ray is frame of right anterior oblique, left ventricular (*LV*) cineangiocardiogram. Dotted line indicates plane of mitral annulus beneath aortic root (*A*) Arrows within the left atrium (*LA*) outline the outer extent of midsystolic posterior leaflet prolapse.

on its longitudinal axis and displacing the left ventricle posteriorly As a result, the right ventricle constitutes the entire anterior surface of the heart including the apex. Such patients present a single diffuse systolic lift (Fig 8 *b*) the left border may extend to the anterior axillary line The examiner may erroneously diagnose biventricular enlargement Palpation may seem to identify a left ventricular impulse however by inching his hand across the precordium the physician will perceive the apparent apical impulse to be part of the diffuse right ventricular movement. The KCG will confirm this identity of contour Angiocardiographic observations confirm the right ventricular origin of the apical impulse in patients with marked ventricular dilatation.

Tricuspid regurgitation of severe degree can also cause widespread precordial lifting extending across the lower right chest wall

The systolic bulge probably derives from paradoxical *systolic expansion of ischemic* or infarcted myocardium Anatomical ventricular aneurysm causes an identical movement Many bulges however do not relate to true aneurysms when studied at autopsy Occasionally this movement occurs an interspace higher than the usual left ventricular impulse high location of a systolic thrust—particularly if medial to the expected LMI—should suggest the bulge of myocardial infarction with or without ventricular aneurysm

Late systolic impulse

The normal lateral precordial kinetocardiogram exhibits a small outward deflection in late systole attributed by Prieto and associates[23] to relaxation and anterior movement of the interventricular septum This movement is not normally felt Occasionally palpable pulsation does occur in late systole When such movement accompanies an early systolic thrust *bifid systolic impulse* results. This double movement must be distinguished from the double movement caused by an atrial thrust followed by early systolic pulsation

Late systolic movement especially characterizes two conditions severe mitral regurgitation and hypertrophic subaortic stenosis.

The late impulse of mitral regurgitation is felt over the sternum and left parasternal region (Fig 10) When vigorous it may extend over the entire precordium including the lower right chest and pulmonic area two-handed palpation may perceive an asynchronous movement pattern composed of an early systolic apical impulse and a late systolic parasternal thrust The latter results from exaggerated left atrial filling which pushes the right ventricle forward as atrial distention peaks in late systole

Hypertrophic subaortic stenosis likewise can cause late systolic apical pulsation Since palpable atrial impulse also occurs in this condition two kinds of double pulsation may develop presystolic and early systolic or early systolic and late systolic [24] Occasionally it is possible to appreciate all three distinct outward movements in hypertrophic subaortic stenosis

The late systolic thrust of hypertrophic subaortic stenosis coincides in time with peak left atrial filling and with relaxation of the hypertrophied septum The exact pathophysiology is not certain The movement is more brisk and localized than that of mitral regurgitation perhaps because the thick walled left atrium of subaortic stenosis seldom enlarges more than slightly and therefore does not displace the heart as much as does the greatly dilated left atrium of severe mitral regurgitation

A 32 year-old man recently underwent cardiac catheterization because of a mid *systolic click and late systolic murmur with* bifid apical systolic impulse Hypertrophic subaortic stenosis was suspected to coexist with a prolapsing mitral leaflet. Diagnostic study confirmed late systolic prolapse of a markedly billowing posterior mitral leaflet with only minimal regurgitation Hypertrophic subaortic stenosis was not present All intracardiac pressures were normal Simultaneous kinetocardiograms and phonocardiograms (Fig 15 *A*) revealed normal early *systolic movement followed by a* striking late systolic outward thrust which peaked at the same instant as the mid systolic click This finding suggested that the outward movement related to the sudden midsystolic tautness of the maximally distended prolapsed leaflet Mild mitral regurgitation began at this point accounting for the late systolic murmur Fig 15 *B* reveals the prolapsed leaflet to occupy a large portion of the left atrial cavity

Diffuse movements

An occasional patient will present diffuse outward systolic movement of the entire lower precordium from apex to sternum Sometimes the movement is truly massive *extending from the left anterior axillary* line to the lower right chest.

Though of varied cause such movements look and feel the same graphic records display similar contour often resembling a ventricular pressure pulse (Fig 16) The significance of such movements therefore must derive from correlated clinical findings.

In right ventricular dilatation (as occurring in volume overloading left-to-right shunts) atrial septal defect and/or anomalous pulmonary venous drainage can produce enormous distention of the right ventricle causing the heart to rotate clockwise

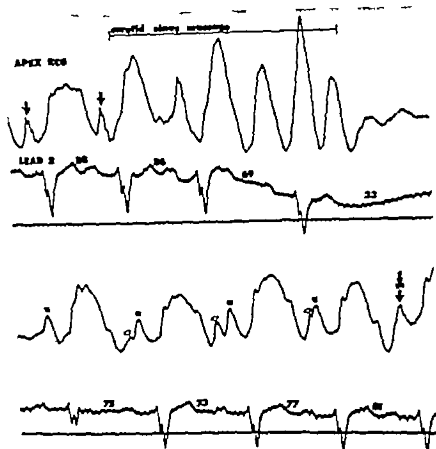


Fig. 17 Continuous apex KCG of 58-year-old man with severe aortic stenosis and P R interval of 0.28. The initial complexes at a heart rate (HR) of 88 per minute have summation diastolic impulses (solid arrows). Following carotid sinus massage, the HR slows to 33 per minute; a presystolic impulse is then seen (lower panel) related to atrial contraction (*a*). At an HR of 73 per minute, the diastolic filling wave (open arrow) distinctly separates from the presystolic atrial impulse (*a*). When the HR again exceeds 80 per minute, these two separate movements fuse or summate, forming a single movement (semi-solid arrow).

This movement resembles other diffuse movements; correlation with history, electrocardiography and roentgenography will usually permit proper interpretation of this form of diffuse impulse.

Extra cardiac masses may displace the heart forward, exaggerating all chest-wall movement. Recently a 56-year-old man presented a heaving precordial systolic thrust which extended from the left anterior axillary line across the midline into the right chest. He had a large aneurysm of the descending thoracic aorta directly behind the heart.

Other movements

Some patients with ventricular gallop rhythm have sufficiently vigorous early diastolic rapid filling waves as to be palpable. The tactile sensation is very brief so that a gentle thrust is felt rather than an actual lifting sensation. The movement may be confused with the atrial impulse, just as atrial and ventricular gallops are confused on auscultation. Fig. 17 illustrates fusion or summation of the early diastolic rapid filling and atrial impulses into a single outward movement. This phenomenon resulted from the association of rapid heart rate and P R prolongation; the two impulses separated following slowing induced by carotid sinus pressure.

Unusually vigorous pulsation arising from a dilated pulmonary artery may cause a discrete pulmonic midsystolic impulse. At times this movement is better seen than felt. However, most palpable movements in the pulmonic area have similar contour

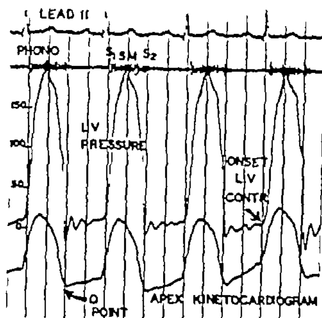


Fig 16 Systolic thrust of advanced left ventricular disease closely resembles left ventricular pressure pulse. Note close similarity of simultaneously recorded kinetocardiogram and left ventricular pressure curve.

as well Unless left ventricular disease coexists advanced tricuspid regurgitation causes apical retraction [18]

Severe pulmonary hypertension may cause diffuse systolic movement though not as massive as that of the chronic volume over loaded right ventricle Fig 9 exhibits the tracings of a young woman with far advanced primary pulmonary hypertension This patient presented diffuse precordial pulsation which included the pulmonic area

Left ventricular dilatation may also cause a diffuse systolic precordial lift Advanced chronic mitral regurgitation may cause counterclockwise rotation of the heart on its longitudinal axis causing the left ventricle to occupy most of the anterior cardiac surface The impulse in these patients may extend from apex to right lower chest wall

Combined ventricular hypertrophy causes a typical movement pattern which combines the sustained left parasternal movement of right ventricular hypertrophy with the abnormal apical thrust of left ventricular enlargement.

Ventricular septal defect with large left to-right shunt and pulmonary hypertension often exemplifies the impulse pattern of combined hypertrophy causing a displaced and overactive apical impulse with a more diffuse sustained left parasternal lift. Between these two movements there is a zone of diminished pulsation where the medial and lateral precordial impulses blend

Primary myocardial diseases also involve both ventricles. Patients in the late stages frequently have functional mitral and tri cuspid regurgitation and congestive heart failure with marked dilatation of both ventricles as well as both atria. Such patients may present a diffuse precordial systolic lift from apex to sternum and right chest The genesis of such movement may be difficult to state with certainty since all four dilated chambers may contribute occasionally such patients also have systolic-hepatic pulsations due to tricuspid regurgitation

Many patients with primary myocardial disease however have an apical thrust with parasternal systolic retraction even late in the disease when advanced cardiomegaly exists This movement pattern may be mistaken for that of combined hyper trophy unless the movements are carefully timed. Bimanual palpation will reveal the asynchrony of the apical and parasternal impulses in such cases.

Ventricular aneurysm usually causes a localized bulge as discussed earlier Occa sionally a large aneurysm may produce systolic lifting of the entire precordium

REFERENCES

1. Dressler W Pulsations of the wall of the chest, Arch. I tern. Med. 60:225 1937
2. Dimond, E., Duenas, A., and Benchimol, A.: Apex cardiography Amer. Heart J 72:124 1966.
3. Eddleman, E. Willis, K., Reeves, T and Harrison T The kinetocardiogram. I Method of recording precordial movements, Circulation 8:269 1953
4. Eddleman, E Willis, K., Christianson, L. Pierce, J nd Walker R. The kinetocardiogram. II The normal configuration and amplitude Circulation 8:370, 1953
5. Hurst, J and Blackard E. Inspection and palpation on the front of the chest, Amer. Heart J 56 159 1958.
6. Norman, J and Harrison, T Movements and forces of the human heart. IV Precordial movements (kinetocardiograms) in relation to ejection and filling of the entricles, Arch. Intern. Med. (Chicago) 101:582, 1958.
7 Deliyannis, A., Gillam, P Mounsey J and Steiner R. The cardiac impulse and the motion of the heart, Brit. Heart J 26:396, 1964.
8. Tootoonis, P and Shillingford, J Impulse cardiogram in early diagnosis of left ventricular dysfunction in hypertension, Brit. Heart J 31:97 1969
9 Davie, J Langley J Dodson, W and Eddleman, E. Clinical and kinetocardiographic studies of paradoxical precordial motion, Amer. Heart J 63 775 1962.
10. Bancroft, W and Eddleman, E. Methods nd physical characteristics of the kinetocardiographic and apexcardiographic systems for recording low-frequency precordial motion, Amer. Heart J 73 756, 1967
11 Sutton, G Prewitt, T and Craige, E Relationship between quantitated precordial movement and left entricular function, Circulation 41 179 1970.
12. Boicourt, O Nagle, R., and Mounsey J The clinical significance of systolic retraction of the apical impulse, Brit. Heart J 27:379 1965
13. Eddleman, E., and Thomas, H. The recognition and differentiation of right entricular pressure and flow loads, Amer J Cardiol. 4:652 1959.
14 Gillam, P Deliyannis, A., and Mounsey J The left parasternal impulse, Brit. Heart J 26 726, 1964
15. Holt, J and Eddleman, E.. The precordial movements I adults with pulmonic stenosis, Circulation 35:492 1967
16. Dressler W.. Precordial heave on the right related to left-atrial enlargement, J.A.M A. 205:96, 1968.
17 Mounsey P Precordial pulsations in relation t cardiac movement and sounds, Brit. Heart J 21:157 1959
18. Mounsey J Inspection and palpation of the cardiac impulse Progr Cardiovasc. Dis. 10 187 1967
19 Eddleman, E., and Harrison, T The kinetocardiogram in patients with ischemic heart disease Progr Cardiovasc. Dis. 6 189 1963
20. Sch ezer W Bertrab, R., and Reirt, P H.. Kinetocardiography in coronary artery disease, Brit. Heart J 27:263 1965.
21. Stapleton, J and Lindberg B. Atrial pulsation of the chest wall, Med. Ann. D C. 36:514, 1967
22. Eddleman, E. Kinetocardiographic changes in ischemic heart disease, Circulation 32:650, 1965.
23 Prieto, G., Coghlan, C., and Harrison, T.. Movements of the heart during the period between the onset of relaxation and the beginning of entricular filling Amer. Heart J 62:528, 1961.
24. Nagle, R., Boicourt, O Gillam, P and Mounsey J Cardiac impulse in hypertrophic obstructive cardiomyopathy Brit. Heart J 28:419 1966.
25. Malloch, C., Abbott, J and Rapaport, E. Left trial myxoma ith bacteremia, Amer J Cardiol. 25:353, 1970.

to those recorded in the left lower parasternal area and represent the periphery of a diffuse right ventricular systolic lift (Fig 9) or the left atrial filling movement of *mitral regurgitation* (Fig 10)

A recent report attributes a bifid early systolic thrust to left atrial myxoma ascribing the initial impulse to movement of the tumor during isometric contraction the *second impulse then* representing the normal apex movement [23]

Summary

Precordial palpation is a simple useful part of the physical examination Although practiced for centuries only recently have recording methods clarified the meaning of various movement patterns.

Informative palpation requires careful *attention to such movement characteristics* as location timing duration and amplitude Preliminary inspection is indispensable as is simultaneous auscultation and palpation

The apical impulse is normally a left ventricular pulsation Abnormality usually indicates left ventricular enlargement Volume-overloading conditions such as aortic regurgitation cause a brisk systolic impulse which *is displaced to the left* Pressure-overloading conditions such as aortic stenosis cause less displacement but lead to a more sustained systolic impulse Occasionally the impulse of left ventricular *pressure overload* extends to the lower left parasternal area

Right ventricular hypertrophy due to pulmonary hypertension causes a diffuse lower left parasternal systolic impulse The right ventricular dilatation of atrial septal defect causes an overactive systolic impulse in the same location which is sustained only when pulmonary hypertension coexists The right ventricular impulse of *mitral stenosis* is more medial than other right ventricular conditions often maximal over the lower sternum The right ventricular impulse of pulmonic *stenosis* is often greatest in the left midclavicular line

Severe volume overloading of the right ventricle may lead to diffuse systolic outward movement extending even to the anterior axillary line The outer edge of this movement can simulate a left ventricular apical impulse.

Conditions which increase resistance to ventricular filling cause prominent atrial impulses Such diseases as aortic stenosis pulmonic stenosis hypertension (systemic and pulmonary) myocardial infarction and primary myocardial disease may give rise to palpable atrial thrust which can simulate ventricular systolic *movement* Primary myocardial disease in particular can lead to a giant atrial impulse palpable across the precordium Congestive heart failure of any cause may also exaggerate atrial movement

Double pulsations characterize several conditions Most commonly this results from palpable atrial and ventricular systolic impulses Mitral regurgitation may cause late systolic parasternal movement distinguishable from the early systolic thrust of left ventricular dilatation *Hyper*trophic subaortic stenosis may also cause more than one pulsation consisting of atrial and/or early systolic and/or late systolic pulsation(s)

Other causes of abnormal *systolic pulsa*tion include acute myocardial infarction ventricular aneurysm retrocardiac masses and extra cardiac deformities which cause cardiac displacement

A patient is reported who has a double systolic impulse at the apex associated with a billowing posterior mitral leaflet We propose that the late systolic apical impulse relates to the late systolic prolapse *of the posterior* leaflet

Occasionally marked systolic retraction with abrupt diastolic rebound may if mistimed resemble an abnormal systolic pulsation Restrictive myocardiopathy and constrictive pericarditis may cause this movement pattern Occasionally a hyperkinetic but otherwise normal left parasternal retraction may present a *diastolic* rebound which is mistaken for an abnormal systolic thrust

Graphic records of precordial pulsation have much value supplemental to palpation and *should be readily* available to those who evaluate cardiac patients as well as to all physicians and students engaged in the study of physical *diagnosis.*

We wish to acknowledge with appreciation the assistance of Dr W Procter Harvey D Bruce Lindberg, Dr Keith Lindgren, Dr James Ronan, Mr Bernard Salb, and Miss Georgia Mallin.

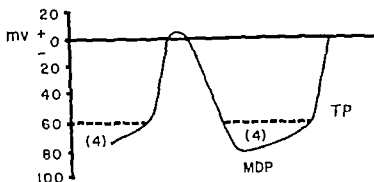


Fig. 1. Diagrammatic representation of transmembrane action potential for a single fiber of the sinoatrial node. Note the maximal diastolic potential (*MDP*) of −80 mv and spontaneous depolarization during Phase 4 which lowers the membrane potential to threshold potential (*TP*) of −60 mv. At threshold, spontaneous firing occurs and is followed by repolarization. The rate of firing may be decreased by a decrease in the slope of Phase 4 depolarization, an increase in the *MDP* (i.e., larger negative value) a decrease in *TP* or any combination of these. Rate may be increased by the opposite change in these variables. (Modified after Hoffman and Singer: Ann. N. Y. Acad. Sci. 139:916, 1967.)

is that period during which a cell cannot generate a propagated response to a normal stimulus (Fig. 2). From the end of the effective refractory period to completion of repolarization a premature stimulus will elicit an abnormal response. Such a response will have a lower than normal velocity of depolarization during the upstroke of the action potential (V of Phase 0) a reduced amplitude, and hence a decreased conduction velocity. As full repolarization is approached upstroke velocity action potential amplitude, and conduction improve. A premature impulse propagating before full electrical recovery has occurred may undergo decrement and block with a resultant arrhythmia.

the mechanisms discussed thus far are ...rtant in the genesis of cardiac arrhyth... the ideal antiarrhythmic drug in ...apeutic doses should probably (1) de...se the slope of Phase 4 depolarization ...ctopic pacemaker cells, thus decreasing ...maticity of aberrant foci (2) either have ...ffect on V of Phase 0 or else increase this ...able in diseased tissues, hence improv... conduction (3) enhance or at any rate ... depress, atrioventricular and intra...tricular conduction and (4) prolong the ...ctive refractory period relative to the ...on potential duration in fibers of the ...-Purkinje system and ventricular mus... It is of interest that diphenylhydantoin, ... drug which most closely approximates these requisites, is by no means the most effective antiarrhythmic agent. This is probably due to the fact that additional mechanisms for production of arrhythmias exist beyond those discussed and that many of the means by which pharmacologic agents exert their antiarrhythmic effects have not yet been delineated.

Methods for evaluation of antiarrhythmic agents

The antiarrhythmic effects of drugs are studied with standard electrophysiologic techniques in the following ways: in tissue bath experiments using isolated cardiac specialized fibers and/or muscle fibers, in acute and chronic experiments on intact animals, and in clinical studies. In the tissue bath the transmembrane potential of a single cell or fiber is recorded. Changes seen in maximal diastolic potential and Phase 4 depolarization reflect alterations in automaticity while changes in V of Phase 0 and action potential amplitude reflect alterations in conduction. In acute and chronic experiments on animals epicardial and endocardial electrodes are used to determine the effect of drugs on conduction during sinus rhythm or induced arrhythmias. Finally in clinical studies, the effects of drugs on patients exhibiting arrhythmias may be noted and compared to their efficacy in the laboratory.

When interpreting the effects of anti

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Julian Frieden

Antiarrhythmic drugs

Michael R. Rosen, M.D.
Henry Gelband, M.D.
New York, N.Y.

The commonly used antiarrhythmic agents—quinidine, procaine amide, diphenylhydantoin, lidocaine, and propranolol—are of undoubted efficacy in the management of selected cardiac arrhythmias. All share certain characteristic actions deemed significant for antiarrhythmic effect; however, there are differences in their effects on electrophysiologic properties of cardiac cells which modify the indications for their clinical use. The following discussion presents the mechanism of action of these agents, as well as two drugs of as yet uncertain value, bretylium tosylate and phentolamine. Emphasis is placed on observations made in experiments on their effects on electrophysiologic properties of the heart and the clinical applicability of these observations.

Genesis of cardiac arrhythmias

In the normal heart, impulses initiated periodically in the sinoatrial node are conducted to other parts of the heart by the specialized conducting system. These impulses are the result of the automaticity of the sinoatrial node fibers, automaticity being an inherent property arising from spontaneous, gradual depolarization of the resting cell membrane during Phase 4 of the action potential. Automaticity is a property not only of the sinoatrial node but of most if not all of the specialized conducting system, a network which includes the interatrial and internodal conducting fibers, the N-H region of the atrioventricular junctional area, and the His-Purkinje system. When normal automaticity is disturbed, due to changes in rate of discharge of the sinoatrial node or to escape of one or more competing atrial or ventricular pacemakers, arrhythmias may occur.[1,2] Such changes in automaticity, whether induced by abnormalities in ionic balance, pH, oxygenation, hormonal factors, stretch, or drug administration, are reflected in the action potential by changes in the rate of Phase 4 depolarization with or without attendant changes in resting and threshold potential (Fig. 1).[1,3]

Another cause of arrhythmias, which may operate either by itself or in combination with altered automaticity, is abnormal conduction. This may occur when the normal time course of depolarization and repolarization is disturbed or when normal pathways of conduction are bypassed, causing acceleration or delay in the propagation of a given impulse. Whether or not an impulse propagates is dependent on the effective refractory period of the cells it encounters. The effective refractory period

From the Department of Pharmacology, College of Physicians and Surgeons, Columbia University, New York, N. Y.
This review was written during Dr. Rosen's tenure as a Postdoctoral Fellow supported by the New York Heart Association, and Dr. Gelband's tenure as a Special Postdoctoral Research Fellow supported by the National Heart Institute (HE-42457).
Reprint requests to: Michael R. Rosen, M.D., Department of Pharmacology, College of Physicians and Surgeons, 630 West 168th St., New York, N. Y. 10032.

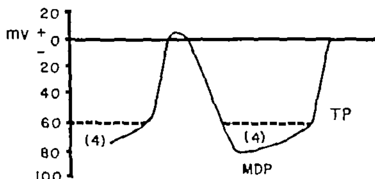


Fig. 1 Diagrammatic representation of transmembrane action potential for single fiber of the sinoatrial node. Note the maximal diastolic potential (*MDP*) of −80 mv and spontaneous depolarization during Phase 4 which lowers the membrane potential to threshold potential (*TP*) of −60 mv. At threshold, spontaneous firing occurs and is followed by repolarization. The rate of firing may be decreased by decrease in the slope of Phase 4 depolarization, an increase in the *MDP* (i.e., larger negative value) decrease in *TP* or any combination of these. Rate may be increased by the opposite change in these variables. (Modified after Hoffman and Singer Ann. N Y Acad Sci. 139:916, 1967.)

is that period during which a cell cannot generate a propagated response to a normal stimulus (Fig. 2). From the end of the effective refractory period to completion of repolarization a premature stimulus will elicit an abnormal *response*. Such a response will have a lower than normal velocity of depolarization during the upstroke of the action potential (V of Phase 0) a reduced amplitude, and hence a decreased conduction velocity. As full repolarization is approached upstroke velocity action potential amplitude, and conduction improve. A premature impulse propagating before full electrical recovery has occurred may undergo decrement and block with a resultant arrhythmia.

If the mechanisms discussed thus far are important in the genesis of cardiac arrhythmias, the ideal antiarrhythmic drug in therapeutic doses should probably (1) decrease the slope of Phase 4 depolarization in ectopic pacemaker cells, thus decreasing automaticity of aberrant foci (2) either have no effect on V of Phase 0 or else increase this variable in diseased tissues, hence improving conduction (3) enhance or at any rate not depress, atrioventricular and intraventricular conduction, and (4) prolong the effective refractory period relative *to the* action potential duration in fibers of the His-Purkinje system and ventricular muscle. It is of interest that diphenylhydantoin the drug which most closely approximates these requisites, is by no means the most effective antiarrhythmic agent. This is probably due to the fact that additional mechanisms for production of arrhythmias exist beyond those discussed and that many of the means by which pharmacologic agents exert their antiarrhythmic effects have not yet been delineated.

Methods for evaluation of antiarrhythmic agents

The antiarrhythmic effects of drugs are studied with standard electrophysiologic techniques in the following ways: in tissue bath experiments using isolated cardiac specialized fibers and/or muscle fibers, in acute and chronic experiments on intact animals, and in clinical studies. In the tissue bath the transmembrane potential of a single cell or fiber is recorded. Changes seen in maximal diastolic potential and Phase 4 depolarization reflect alterations in automaticity while changes in V of Phase 0 and action potential amplitude reflect alterations in conduction. In acute and chronic experiments on animals epicardial and endocardial electrodes are used to determine the effect of drugs on conduction during sinus rhythm or induced arrhythmias. Finally in clinical studies, the effects of drugs on patients exhibiting arrhythmias may be noted and compared to their efficacy *in the laboratory*.

When interpreting the effects of anti

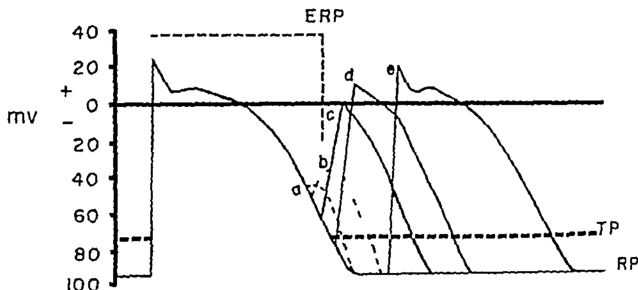


Fig 4 Normal transmembrane action potential of a Purkinje fiber and responses to a series of stimuli delivered during and after depolarization. Graded responses, *a* and *b* do not propagate. The earliest propagated response is *c*, which defines the end of the effective refractory period (ERP) Response (*d*) occurs when membrane potential is close to threshold potential i.e., during the supernormal period of excitability Response (*e*) occurs after full repolarization. Amplitude is normal and rate of depolarization approaches normal. (Modified after Hoffman and Singer Ann. N Y Acad Sci 139:919 1967)

arrhythmic drugs on electrophysiologic properties of the heart one must be cognizant of several complicating factors. (1) Different areas of the heart may respond differently to the same drug concentration (e.g the effect of diphenylhydantoin on atria and ventricles differs markedly) (2) In general muscle tissue may not be affected by a drug concentration sufficient to act on specialized tissues [3] (3) Reports of drug effects on Purkinje and ventricular muscle fibers rest on more concrete laboratory evidence than those dealing with atrial and junctional tissues, due to more extensive study of the former

Antiarrhythmic drugs

A summary of the major electrophysiologic effects of antiarrhythmic drugs is presented in Table I Two major group effects are apparent those seen with quinidine and procaine amide and those seen with diphenylhydantoin and to a lesser extent, lidocaine. Propranolol has properties common to both groups.

Quinidine and procaine amide Although quinidine is more potent in equimolar dosage [3] both drugs exert similar electrophysiologic effects and are therefore discussed together In therapeutic doses quinidine and procaine amide slow conduction velocity throughout the heart[4,7] without significantly affecting sinus rate.[8] Action potential duration of sinoatrial node cells is unchanged or prolonged and in these cells Phase 4 shows no significant change.[4,8] The major effect of these drugs on atrial myocardium is to decrease V of Phase 0 and prolong repolarization [3]

In Purkinje fibers the slope of Phase 4 is depressed prior to other effects upon the action potential [3,5,4] V of Phase 0 is decreased while threshold and resting potential are usually unchanged [4,6] Both action potential duration and effective refractory period are prolonged the latter more than the former [3,4] The over all effect here is relative prolongation of the effective refractory period which should modify the usual relationship between conduction and refractoriness in re-entrant circuits (in the sense that the earliest conducted response will be more nearly normal) This effect may be important in abolishing arrhythmias generated in this manner On the other hand depression of conduction may lead to adverse effects such as decremental conduction or block in previously normal cardiac tissues, producing manifestations of quinidine toxicity

The antiarrhythmic action of quinidine almost certainly is due to its effect on the

cell membrane but the nature of this effect is uncertain. Quinidine binds weakly to membrane lipid or lipoprotein several theories concerning its action here have been advanced.[3] First, a positive charge on the free tertiary nitrogen of the quinidine molecule could repel cations such as sodium and potassium which otherwise would cross the cell membrane. In support of this thesis is the fact that sodium influx during depolarization and potassium efflux during repolarization are said to be decreased when cells are poisoned with quinidine.[3] Second the positively charged quinidine molecule might attract the negatively charged dipole of water increasing the hydration (and thickness) of the membrane and slowing ionic diffusion Third by chelating calcium quinidine may block the passage of this ion through the membrane.

Diphenylhydantoin. Therapeutic concentrations of diphenylhydantoin have no significant effect on sinus rate or conduction within the atrium. [7] In normal hearts atrioventricular and intraventricular conduction time are unaffected by diphenylhydantoin except when higher doses are infused, in which case the former may be prolonged. On the other hand if atrioventricular or intraventricular conduction times have been prolonged by digitalis or procaine amide, diphenylhydantoin tends to increase conduction velocity in these specialized tissues.[7]

The single most striking effect of diphenylhydantoin on atrial conducting tissue and atrial muscle is the production of a marked increase in V of Phase 0 of the action potential an effect which is especially prominent when these tissues have been depressed with digitalis. This change usually is associated with an increase in conduction velocity and might be one reason for the greater efficacy of diphenylhydantoin in the treatment of digitalis-induced atrial arrhythmias as compared to other atrial arrhythmias.

In normal Purkinje fibers, the resting potential and V of Phase 0 are unchanged by diphenylhydantoin In partially depolarized Purkinje fibers, however both are increased.[10] The slope of Phase 4 of the Purkinje fiber action potential is depressed a factor which may contribute to decreasing automaticity in ectopic foci.[10] Finally diphenylhydantoin shortens action potential duration and effective refractory period the former more than the latter resulting in a relative prolongation of the effective refractory period [9]

The effect of diphenylhydantoin on transmembrane ionic flux has not been fully investigated. One experiment on rat heart suggests that diphenylhydantoin brings about loss of sodium from cardiac cells.[11] This sodium loss may be accompanied by increased potassium influx[12] this might result from improved function of the sodium pump mechanism and could conceivably return a partially depolarized cell to its normal resting potential

Comparison of diphenylhydantoin to quinidine brings out the obvious similarities and differences between the effects typical of drugs in each of the two groups previously mentioned Both decrease susceptibility of cells to the effects of premature stimuli by causing a relative (diphenylhydantoin) or absolute (quinidine) prolongation of the effective refractory period. Both decrease automaticity by depression of Phase 4 depolarization The major difference is that, by enhancing conduction velocity diphenylhydantoin should abolish decremental conduction and re-entrant arrhythmias. A complicating factor of at least theoretical validity is that while diphenylhydantoin improves conduction in some diseased areas of the heart, it might by the same mechanism permit arrhythmias to develop in other abnormal areas where ectopic impulses were previously produced but were not of sufficient amplitude or velocity to be propagated [13]

Lidocaine Therapeutic doses of lidocaine have no effect upon sinus rate atrial conduction, or the sinoatrial node action potential [4,14] Higher doses may cause slowing of the spontaneous sinoatrial rate and conduction block between sinoatrial node and atrial specialized fibers. Atrioventricular and intraventricular conduction usually are unaffected by lidocaine. [4] At the Purkinje fiber–ventricular muscle junction however lidocaine has been reported to accelerate conduction thereby abolishing unidirectional and bidirectional block.[17]

In Purkinje fibers, "therapeutic concentrations of lidocaine do not change V of Phase 0 of the action potential, threshold,

or resting potential[8,18] Effects on Phase 4 of the action potential the effective refractory period and action potential duration are like those of diphenylhydantoin The mechanism of action of lidocaine at the cellular level has not yet been elucidated

Propranolol Propranolol has electrophysiologic actions common to both groups of antiarrhythmic agents discussed and is a potent beta-adrenergic blocker as well The commercially available drug consists of equal proportions of dextro- and levorotatory stereoisomers. Beta adrenergic blockade is largely an effect of the *l* isomer while both forms have significant antiarrhythmic activity[19]

Propranolol decreases sinus rate[20] the only antiarrhythmic agent to do so at therapeutic dose levels, and prolongs atrial and atrioventricular conduction time[21] In atrial muscle V of Phase 0 is decreased repolarization is accelerated while resting potential remains unchanged[13] In Purkinje fibers propranolol decreases V of Phase 0 and conduction velocity as does quinidine while it shortens action potential duration and effective refractory period in a fashion similar to diphenylhydantoin[18,19,21,22] The slope of Phase 4 of the action potential is depressed while resting potential is unchanged or decreased[18,19,22] Propranolol is said to bind at the sarcoplasmic reticulum where it may depress calcium transport[19] The relationship of this to its basic antiarrhythmic effect is not certain

Bretylium tosylate and phentolamine These drugs are considered together only for convenience in presentation Bretylium blocks postganglionic sympathetic nerve transmission and releases norepinephrine from both ganglia and postganglionic nerve sites as it binds to them[23] Few data are available concerning its electrophysiologic effects on the heart One study on atrial muscle has shown no change in action potential characteristics when therapeutic concentrations of bretylium were infused[24] Another study has demonstrated that intraventricular conduction is also unaffected[25]

In the Purkinje system there is no change in V of Phase 0 of the action potential and either no change[24] or an increase[24] in the slope of Phase 4 depolarization. This effect dissimilar to all antiarrhythmic drugs, is not unlike that of catecholamines. Purkinje fiber resting potential is reportedly unchanged or increased[24] Although action potential duration and effective refractory period are prolonged there is no net prolongation of effective refractory period with relation to action potential duration[25,26]

Phentolamine has been described as useful in the treatment of clinical cardiac arrhythmias[27] but has not yet been studied utilizing electrophysiologic techniques. Infusion of 300 μg per minute reportedly decreases the incidence of ventricular arrhythmias without causing the alpha-adrenergic blockade with which phentolamine is usually associated[27] However the rate of metabolism of phentolamine is uncertain and it is conceivable that a twenty minute infusion at the rate described could have at least some alpha blocking effect. What makes this point interesting is that maximal alpha blocking doses of phentolamine have been shown to increase norepinephrine synthesis in rat heart.[28]

If phentolamine and bretylium both in fact increase the availability of endogenous catecholamines to the heart it may be that they act at least in part in a manner totally opposed to other antiarrhythmic drugs Catecholamines are known to cause hyperpolarization of partially depolarized or sick fibers. The result is restoration of a normal action potential configuration without significant change in Phase 4 By this means catecholamines may increase conduction velocity through areas where abnormal conduction is occurring and hence abolish arrhythmias[29] It is conceivable that at least part of the antiarrhythmic action noted with phentolamine and bretylium may be secondary to such a mechanism

Efficacy of drugs in treatment of arrhythmias

Only propranolol quinidine and to a lesser extent procaine amide are of proven use in the treatment of atrial arrhythmias[5,30] When digitalis-induced atrial arrhythmias are considered diphenylhydantoin is a significant addition[31] All drugs listed are useful in the management of ventricular arrhythmias, with lidocaine and diphenylhydantoin probably of greatest

efficacy in those arrhythmias that are digitalis induced.[illegible]

Clinical studies of bretylium tosylate are contradictory. Several available reports suggest it is useful in treatment of ventricular arrhythmias.[illegible] However, a recent study demonstrated that bretylium was ineffective in preventing ventricular arrhythmias in patients with myocardial infarcts, although its use was associated with a decrease in atrial arrhythmias in the same patients.[illegible] As has already been mentioned, limited electrophysiologic data have shown bretylium to be dissimilar to other antiarrhythmic drugs.[illegible] This point, coupled with the conflicting reports concerning its clinical efficacy, make it impossible to adequately assess the usefulness of bretylium at the present time.

Phentolamine has been the subject of even less study than bretylium. Further evaluation of its clinical effects and electrophysiologic actions is awaited.

Toxicity

Myocardial depression, hypotension, and bradyarrhythmia with or without heart block are major cardiotoxic effects of these drugs. When equivalent doses are studied, propranolol, lidocaine, procaine amide, quinidine, and diphenylhydantoin, in that approximate order, all exert negative inotropic effects.[illegible] The depressant effect of diphenylhydantoin is probably equal in degree to, but of shorter duration than, that of quinidine and procaine amide.[illegible] Propranolol is the only agent that consistently has a negative inotropic action in therapeutic doses, and therefore is the most formidable myocardial depressant used clinically,[illegible] whereas lidocaine, which is administered in smaller doses than the other drugs, shows the least cardiodepressant effect in clinical use.

Hypotension may occur secondary to myocardial depression and/or peripheral vasodilatation. All agents except bretylium have been shown to exert both effects.[illegible]

Bradyarrhythmias and/or heart block, when they occur, are probably due to a combination of (1) the decrease in automaticity seen with the major drugs discussed, (2) the decrease in conduction velocity throughout the conducting system seen with the quinidine group, and at the atrioventricular junctional region observed occasionally with diphenylhydantoin[7] and (3) the specific beta-adrenergic blocking effect of propranolol.

An additional factor contributing to diphenylhydantoin toxicity is the commercial diluent in which it is administered. Because diphenylhydantoin is relatively insoluble in the physiologic pH range, a diluent of 40 per cent propylene glycol, 10 per cent ethanol, and pH adjusted to 11 is required. When infused into cats at one to three times the per kilogram dose used in man, the diluent causes marked sinus bradycardia, hypotension, and electrocardiographic abnormalities consisting of changes in QRS and T wave configuration.[34]

Several reports suggest there is no significant toxic effect with clinical use of phentolamine and bretylium.[illegible] However, a recent study on the latter drug states that one third of the patients to whom bretylium was administered developed hypotension severe enough to necessitate its discontinuation.[illegible] These observations await further verification.

The authors express their appreciation to Dr. Brian F. Hoffman for his advice and critical review of this manuscript.

REFERENCES

1. Hoffman, B. F., and Cranefield, P. F.: The physiological basis of cardiac arrhythmias, Amer. J. Med. 37:670, 1964.
2. Hoffman, B. F.: The possible mode of action of antiarrhythmic drugs, *in* Briller, S. A., and Conn, H. L., Jr., editors: The myocardial cell, Philadelphia, Pa., 1966, University of Pennsylvania Press, p. 251.
3. Conn, H. L., Jr.: Some considerations of quinidine and procaine amide action at the cellular level, *in* Briller, S. A., and Conn, H. L., editors: The myocardial cell, Philadelphia, Pa., 1966, University of Pennsylvania Press, p. 269.
4. Vaughan-Williams, E. M.: The mode of action of quinidine on isolated rabbit atria interpreted from intracellular potential records, Brit. J. Pharmacol. 13:276, 1958.
5. Bigger, J. T., Jr., and Heissenbuttel, R. H.: The use of procaine amide and lidocaine in the treatment of cardiac arrhythmias, Progr. Cardiovasc. Dis. 11:515, 1969.
6. Scherlag, B. J., Helfant, R. H., and Damato, A. N.: The contrasting effects of diphenylhydantoin and procaine amide on A-V conduction in the digitalis-intoxicated and normal heart, Amer. Heart J. 75:200, 1968.
7. Sasyniuk, B. I., and Dresel, P. E.: The effect of diphenylhydantoin on conduction in isolated,

blood perfused dog heart J Pharmacol Exp Ther 161:191 1968.

8. Hoffman B. F and Cranefield P Electrophysiology of the heart New York, 1960 McGraw Hill Book Company Inc.
9. Strauss, H C. Bigger J T Jr., Bassett A L., and Hoffman B F Actions of d phenylhydantoin on the electrical properties of isolated rabbit and canine atria Circ Res. 23:463 1968.
10. Bigger J T Jr Bassett A. L. and Hoffman, B F Electrophysiological effects of diphenylhydantoin on canine Purkinje fibers, Circ. Res. 22:221 1968.
11. Woodbury D M Effect of d phenylhydantoin on electrolyte and radiosodium turnover in brain and other tissues of normal hyponatremic and postictal rats, J Pharmacol. Exp. Ther 115 74 1955
12. Helfant R H and Ricciutti M A. et al Effect of diphenylhydantoin sodium on myocardial AV potassium difference, Amer J Physiol 214:880 1968
13. Hoffman B F Personal communication.
14. Sugimoto T Schaal S F Dunn N M., and Wallace A. G. Electrophysiologic effect of lidocaine in awake dogs J Pharmacol. Exp. Ther 166 146, 1969
15. Morales-Aguilera A. and Vaughan Williams, E. M The effects on cardiac muscle of β-receptor antagonists in relation to their activity as local anesthetics, Brit. J Pharmacol 24:332 1965
16. Mandel W and Bigger J T Jr Effect of lidocaine on sinoatrial node and atrial fibers, Amer J Cardiol 25(Suppl I) 113 1970
17. Bigger J T Jr and Mandel W J Effect of lidocaine on conduction in canine Purkinje fiber and ventricular muscle-Purkinje fiber junction, Circulation 40(Suppl III):III 1969 (Abstr)
18. Davis, L. D and Temte J V Electrophysiological action of lidocaine on canine ventricular muscle and Purkinje fibers, Circ. Res 24:639 1969
19. Shinebourne, E White R and Hamer J A qualitative distinction between the β-receptor blocking and local anesthetic actions of antiarrhythmic agents, Circ. Res. 24:835 1969
20. Benaim J Sozutek Y et al Haemodynamic effects of intravenous propranolol in normal human subjects, Acta Cardiol 23:487 1968.
21. Whitsett L. S. and Lucchesi, B R Effects of β-receptor blockade and glucagon on the atrioventricular transmission system in the dog Circ. Res. 23:585 1968.
22. Davis, L. D and Temte, J V Effects of propranolol on the transmembrane potentials of ventricular muscle and Purkinje fibers of the dog, Circ. Res. 22:661 1968.
23. Green A. F Antihypertensive drugs, *in* Garattini S. and Shore, P editors Advances in pharmacology Vol. 1 New York, 1962, Academic Press, Inc. p. 188.
24. Papp, J and Vaughan-Williams, E. M The effect on intracellular atrial potentials of bretylium in relation to its local anesthetic potency Brit. J Pharmacol 35:352, 1969 (Abstr)
25. Jaffe C. C. and Bigger J T Jr Effect of bretylium tosylate on canine Purkinje and ventricular muscle fibers, Circulation 40(Suppl. III):III 1969 (Abstr)
26. Wit, A. L Steiner C. and Damato, A. N Electrophysiologic effects of bretylium tosylate on single fibers of the canine specialized conducting system and ventricle, J Pharmacol. Exp. Ther 173:344 1970.
27. Gould L. Zahir M et al Treatment of cardiac arrhythmias with phentolamine, AMER. HEART J 78:189 1969
28. Dairman W Gordon, R et al. Effect of alpha blockers on catecholamine biosynthesis, Fed. Proc. 27:240 1968.
29. Hoffman B F and Singer D Appraisal of the effects of catecholamines on cardiac electrical activity Ann. N Y Acad Sci. 139:914, 1967
30. Gibson D and Sowton, E. The use of beta-adrenergic receptor blocking drugs in dysrhythmias, *in* Friedberg C. K editor Current status of drugs in cardiovascular disease New York, 1969 Grune & Stratton Inc. p. 160.
31. Damato, A N Diphenylhydantoin Pharmacological and clinical use *in* Friedberg C. K., editor Current status of drugs in cardiovascular disease New York, 1969 Grune & Stratton Inc p. 145
32. Bacaner M B Treatment of ventricular fibrillation and other acute arrhythmias with bretylium tosylate Amer J Cardiol 21:530, 1968.
33. Taylor S. H Saxton C Davies, P S., and Stoker J B. Bretylium tosylate in prevention of cardiac dysrhythmias after myocardial infarction, Brit Heart J 32:326, 1970.
34. Asokan, S. K. Frank M J and Regan, T J Assessment of myocardial depression with therapeutic doses of lidocaine and procaine amide, Amer J Cardiol 1:91 1968. (Abstr)
35. Mosey L. and Tyler M D The effect of diphenylhydantoin sodium procaine hydrochloride procaine amide hydrochloride, and quinidine hydrochloride upon ouabain-induced ventricular tachycardia in unanesthetized dogs, Circulation 10:65 1954
36. Louis, S and Kutt H. The cardiocirculatory changes caused by intravenous Dilantin and its solvent AMER. HEART J 74:523 1967

Cardiac arrest during edrophonium administration

The intravenous administration of 10 mg. of edrophonium chloride (Tensilon) has proven valuable in the differentiation of supraventricular tachycardias. No serious complications have been reported with the use of this drug,[1-4] and it therefore has achieved ide clinical use. The present communication documents that the drug can produce long periods of ventricular asystole, and serves as arning gainst unnecessary use of this otherwise useful procedure.

An 81-year-old woman was admitted to the hospital because of dyspnea of 2 weeks duration. Tw years previously the patient had been digitalized because of tr al fibrillation. She as then treated th daily maintenance dose of 0 25 mg. of digoxin. However she took this medication erratically

The blood pressure was 110/70 nd the temperature 98° F The neck veins ere distended Rāles ere heard over the lower lung fields posteriorly The heart was greatly enlarged and the cardiac rhythm was irregular There was no hepatic or splenic enlargement but 1+ pitting edema of the legs was present. An electrocardiogram showed tr al fibrillation with n erage ventricular response of 160 per minute. There were voltage criteria for left ventricular hypertrophy A chest roentgenogram revealed enlarged heart ith accentuated pulmonary vasculature consistent with congesti heart failure.

Significant laboratory findings included hematocrit of 41 per cent, blood urea nitrogen of 32 mg. per 100 ml., serum sodium of 130 mEq potassium of 4.3 mEq., nd chloride of 99 mEq On admission the maintenance dose of digoxin as increased to 0.25 mg. twice day After tw days of this therapy the ventricular response was still 140 per minute. The daily digoxin dose was then increased t 0.25 mg. three

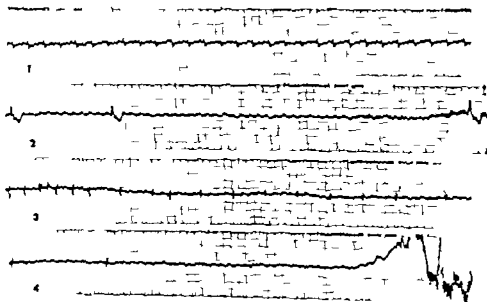


Fig 1 Sequential strips of Lead V taken before (1) and after the administration of edrophonium. Y te the presence of tr al flutter th 2 1 trioventricular block in 1 slowing of the ventricular rate with 10 second period of ventricular systole in 2 and a progressi increase in the atrioventricular block with an 8 second period of entricular asystole in 3 and 4

times a day However after three days little change in the ventricular rate was noted Therefore the patient was placed on 0.25 mg four times a day After three days of this regimen the patient began to vomit and the drug was discontinued At this time the patient had atrial fibrillation with a ventricular response of 120 beats per minute. Two hours after the last dose of digoxin auscultation revealed a regular ventricular response of 150 per minute An electrocardiogram now showed probable atrial flutter at a rate of 300 per minute and a ventricular rate of 150 with a 2 1 atrioventricular conduction For better identification of the arrhythmia 10 mg of Tensilon was injected intravenously Within 2 minutes the atrioventricular block began to increase, and atrial flutter waves were evident on the electrocardiogram However the ventricular rate decreased at an alarming rate and the patient began to complain of dizzy sensations. She lost consciousness during a 10 second period of ventricular asystole Blows to the chest produced transient ventricular systoles but this was shortly followed by another prolonged period of ventricular asystole (Fig 1) Blows to the chest again stimulated ventricular activity and 1 mg of atropine was injected intravenously Atrial fibrillation with a ventricular rate of 160 per minute was now observed. The patient then regained consciousness and had no further complications.

Edrophonium a quarternary ammonium compound acts by inhibiting cholinesterase. Since edrophonium is hydrolyzed by cholinesterase it competes with acetylcholine for this enzyme Edrophonium acts on the cardiac conduction system by potentiating the effect of acetylcholine normally released by the vagi The drug's administration may be expected to produce sinus slowing increased atrioventricular block, and conversion of ectopic atrial tachycardia to normal sinus rhythm In patients with atrial flutter a transient increase of the atrioventricular block occurs after edrophonium administration. This allows identification of the atrial flutter waves.

Our patient was receiving large doses of digitalis, a potent vagomimetic agent which may have potentiated the effects of edrophonium. In addition edrophonium acts in the same manner as carotid sinus stimulation and it is well known that digitalization may sensitize the heart to carotid sinus stimulation.

It is suggested that edrophonium injection be attempted only with clear-cut indications, especially in digitalized patients. During the administration of edrophonium an electrocardiogram should record the drug's effects on the arrhythmia. Adequate facilities for cardiopulmonary resuscitation must be also available.

Lawrence Gould, M.D
Mohammed Zahi M.D
Robert F Gomprecht M.D
Medical Service
Misericordia-Fordham Hospital
600 East 233rd St
Bronx N. Y.

REFERENCES

1. Moss, A J and Aledort, L. M Use of edrophonium (Tensilon) in the evaluation of supraventricular tachycardias, Amer J Cardiol. 17:58, 1966
2. Spitzer S. Mason D Lennon W M and Moyer J H Use of edrophonium (Tensilon) in the evaluation of supraventricular tachycardia Amer J Med Sci. 231 177 1967
3. Hilal H. and Massum R Fatal ventricular fibrillation after carotid sinus stimulation, *New Eng J Med* 275:157 1966.

Meticulous monitoring of all patients

Although much has been said and written about providing the best quality of patient care, relatively little has been done lately to improve the care of patients in open wards and private rooms. A great deal of effort has been expended in developing specialized units for the care of patients with coronary heart disease (coronary care unit or CCU) and of other types of seriously ill people (intensive care unit or ICU) However most patient who die in hospitals do not die in the CCU or ICU but rather in open wards and private rooms. They die of many causes, including cardiac diseases.

Admittedly the value of specialized units such as the CCU is yet to be determined. Nevertheless, some of what has been learned in such units is applicable to the care of patients in the open ward or private room. However the best way to manage all patients in the CCU remains yet to be established What constitutes the best and minimal apparatus and procedures remains unknown If this is still undetermined for the CCU with all of its facilities, nurses, and physicians in attendance the facilities necessary for best care of patients in general medical wards and private rooms certainly have not yet been established

Regardless, existing hospitals, as well as new ones, should be designed to provide constant, proper electronic monitoring with audio and television communication of all patients admitted to the hospital. A central data-receiving console should be made available at all nurses desks and central stations. Nurses and attendants in the wards should

receive the same type of training as the CCU and ICU nurses, attendants, and physicians. Existing electronic monitoring equipment should be carefully studied to be sure that it is simple, minimal, reliable, and relatively inexpensive. Where necessary new equipment must be designed.

There is need, therefore, to design new hospitals and modify existing ones to care *intensively* for *all* patients in the hospital, not only those in special units. The best monitoring devices and well-trained personnel are imperative for the best medical care. Anything less is unacceptable. Remember however regardless of the elegance of apparatus and equipment, well-trained attendants and dedicated doctors and nurses remain imperative for high-quality medical care.

G. E. Burch, M.D
T. D. Giles, M.D
Department of Medicine
Tulane University School of Medicine
New Orleans, La.

Diastolic mitral regurgitation: A pitfall in the angiographic assessment of the mitral valve

Although the left atrial pressure tracing may be quite characteristic in mitral valvular regurgitation, the ability to quantitate this regurgitation by pressure or dye curves may be poor in some patients. In addition, there are patients in whom there is no correlation at all between their pressure curves and the extent of valvular disease. Therefore, left ventricular cineangiography which in itself is only semiquantitative, is the method most often used to determine the extent of mitral valvular regurgitation, especially when surgical procedure is being considered.[1-4] Usually mitral regurgitation is graded on various scales (from mild to severe, one plus to four plus) by the rapidity and the extent to which contrast material enters the left atrium from the left ventricle during systole. However contrast material entering the left atrium at any other time such as during diastole, could contribute to the opacification of this chamber and could lead to an erroneous evaluation of the degree of true systolic mitral regurgitation. This is in addition to any small amount of spurious systolic mitral regurgitation which may but does not always, occur with ventricular premature contractions during the injection of contrast material.

In review of our last fifty left ventricular cineangiograms, diastolic mitral regurgitation was noted on four occasions. Wong[5] described similar incidence, while Honey and associates[6] reported diastolic mitral regurgitation in 12 of 137 angiograms. This over-all 8 per cent incidence is probably an overestimation, as similar review by us two years ago noted 193 consecutive studies with no diastolic mitral regurgitation at all. However in each instance in which we have seen diastolic mitral regurgitation, our fellows, house staff, and students have consistently ascribed the left atrial opacification to true systolic mitral regurgitation and either erroneously diagnosed or overestimated the latter disorder. This error is usually easily rectified following description of the characteristics of diastolic mitral regurgitation.

Late diastolic mitral regurgitation has been described in patients with normal and abnormal mitral valves and is most often seen in long diastolic periods following premature ventricular contraction or in atrial fibrillation.[5-8] It may also occur in complete heart block and in some patients with severe aortic valvular regurgitation in the absence of premature ventricular contractions.[9] In all of these situations, there is reversal of the left atrial-left ventricular pressure gradient during late diastole, which in the absence of firm closure of the mitral valve results in the diastolic overflow of blood back into the left atrium. This pressure reversal has been recorded by Wong in four patients with diastolic mitral regurgitation and atrial fibrillation[5] and is a frequent finding in patients with severe aortic regurgitation where it initiates early mitral valve closure.[10] Whenever the mitral valve is closed by atrial contraction or high left ventricular diastolic pressure, such as in aortic regurgitation, it follows that the valve must be diseased or incompletely closed to allow the regurgitation to occur. It has been shown that although atrial contraction is not essential for closing the mitral valve in all patients, it does help initiate this closure.[11] Atrial systole enhances ventricular filling and during the following atrial relaxation, the reduction in atrial pressure may reverse the diastolic pressure difference between atrium and ventricle and permit the mitral leaflets to move toward the closed position. It is probable, however that only ventricular systole can provide firm closure of the mitral valve. Therefore, when atrial systole is not followed by properly timed ventricular contraction (such as following ventricular premature contraction or heart block) the reversed left atrial-left ventricular pressure gradient permits diastolic mitral regurgitation through an incompletely closed mitral valve.[12,13]

Angiographically this can be seen to occur during late diastole just prior to ventricular contraction, thus eliminating the usual systolic mitral regurgitation as the cause of the left atrial opacification.

In addition, the contrast material appears to float back from the left ventricle to the left atrium like a billowing cloud in contradi tinction to the jet usually seen with systolic regurgitation. With these points in mind the distinction between systolic and diastolic regurgitation is usually easily made, although in patients with multiple ventricular premature contractions the separation may be difficult. However under these circumstances, the assessment of systolic mitral valvular regurgitation may also not be accurate.

Joseph H Linhart, M.D
The University of Texas Medical School at San Antonio
San Antonio Texas
Frank J Hildner M D
Philip Samet M.D
Mt S nai Hospital
Miami Beach Fla

REFERENCES

1 Schlant, R. C Altered cardiovascular function of rheumatic heart disease and other acquired valvular disease Hurst J W and Logue R. B editor The heart New York 1970 McGraw Hill Book Company Inc. p. 757
2 Braunwald E. and Awe W C The syndrome of severe mitral regurg tation with normal left atrial pressure C rcul tion 27:179 1963
3 Ross R S and Criley J M Contrast radiog r phy i mitral regurg tation Progr Cardiovasc Di 8:195 196
4 Sellers, R D Levy M J Amplatz K. and Lillehei, C W Retrograd cardioangiography in acquired cardiac disease Technic ndications and nterpretations of 700 cases Amer J Cardiol. 14:434 1964
5 Wong M Diastolic mitral regurgitation. Haemodynamic and angiographic correlation Brit Heart J 31:468 1969
6 Honey M., Gough J H Katsaros, S. Miller G A. H and Thurnisingham V Left ventricular cineangiography in the assessment of mitral regurgitation Brit. Heart J 31:596 1969
7 Rutishauser W., Wirz, P Gander M and Lüthy E.: Atriogenic diastolic reflux in patients with atrioventricular block Circulation 31:807 1966.
8 Lochaya S. Igarashi, M and Shaffer A. B. Late diastolic mitral regurgitation secondary to aortic regurgitation Its relationship t the Austin Flint murmur AMER. HEART J 71 161 1967
9 Aldridge H E. Lansdown E. I and Wigle E. D Diastolic mitral insufficiency Circulation 34 (Suppl. III) 42 1966.
10 Wigle E. D and Labrosse C. J Sudden severe aortic insufficiency Circulation 32:708, 1965
11 Braunwald E Rockoff S. D Oldham H N and Ross, J Jr Effective closure of the mitral valve without atrial systole Circulation 33:404 1966
12 Braunwald, E. Introduction to symposium on cardiac arrhythmias with comments on the hemodynamic significance of atrial systole, Amer J Med. 37:665 1964
13 Williams, J C I., O Donovan, T I B Vanderberg R A Sturm, R. E and Wood E. H. Atriogenic mitral valve reflux Dia tolic m tral ncompetence following isolated trial sy tole, Circ. Res. 22:119 1968.
14 Vanderberg R L Williams, J C. P Sturm R E. and Wood E. H Effect of ventricular extrasystoles on closure of mitral valve Circulation 39:197 1969

Patient safety during measurement of blood flow*

In recent years techniques of cardiac catheterization have been perfected to the point where these tudies are now done routinely in nearly all hospitals. Yet there are still dangers with these tech iques, among which are the possibil ty of electric shock which has received much attention n the past few years due to the introduction of new techniques such as cardi c pacing, electrically energized flowmeter probes, and other electrical devices which are inserted into a peripheral artery or vein and directed up to the heart. Though most clinicians readily acknowledge these hazards, few of them stop to think that electrically induced ventricular fibrillation can result from a simple saline-filled catheter a ting as l w resi tance pathway from an improperly grounded electrical device uch as the chassis of a polygraph In one widely publicized report it ha been claimed that there are still 1,200 hospital patients each year who die of electrocution. As a result of these dangers linical personnel working in operat ng rooms or catheterization laboratories have justifiably become very reluctant to develop and employ new techniques which might prove dangerous to the patient a well as to himself The present tendency there fore is to try to put the burden of proof of safety upon the companies which manufacture these devices. In one respect this is justified there are reports of excess numbers of electrical devices being defective when received from the factory [1] It would seem to be the ma uf cturer s responsibility to make

*This investigation was supported by United States Public Health Service Grant HE-00487 and HE-4392 and by the North Carolina Heart Association.

sure that his product is in proper working order when delivered. However the manufacturer cannot always control how his product is to be used or what other equipment is to be used with it. It must be the responsibility of the user and his engineering staff to see to it that the equipment is used in a safe manner. It is the purpose of this paper to outline the procedure used in this institution to avoid these hazards in typical diagnostic procedure and to prevent any defects in auxiliary equipment from presenting a danger to patient. For illustration, specific device and manufacturer are described here obviously the same considerations should apply to other devices made by other manufacturers.

The instrument to be discussed here is the catheter tip and direction-sensitive electromagnetic blood flow probe. This catheter has two electrodes and an iron-core electromagnet at its tip which has been made to fit into a 7 F catheter. This device, which measures the velocity of blood flowing past it, is potentially useful to detect and explore intravascular abnormalities such as shunts, aberrant vessels, stenoses, coarctations, valvular deformities and aneurysms or it can be used to map flows through the larger vessels on either the arterial or venous side of the circulation.[7,8] Since it measures either phasic or mean information the first derivative of the aortic velocity pulse can provide valuable cardiac function information. If chronically implanted in patient recovering from surgery or in intensive care unit it could provide continuous information concerning the patient condition.

There have been major objections posed by clinicians which has limited the use of this tool. The first is that this is primarily flow-velocity measuring device and most clinical people prefer to think in terms of volume flow. Though this instrument can be calibrated in terms of volume flow if the sizes of the vessels are known, the present author feels that the velocity data might ultimately prove to be more desirable than the volumetric flow because we have the impression that arteries tend to enlarge to the size that will accommodate their flow without turbulence. For example, under basal conditions, 200 pound man might have cardiac output of 7.5 L per minute and 20 pound child output of 750 ml/minute yet since their aortas would be of considerably different sizes they might have the same flow velocity. Therefore if this speculation is true, abnormal values would be more easily recognized.

The second objection to this instrument, voiced by the clinical people, is the potential electrical danger to the patient resulting from damaged probe. This objection is certainly valid one and one which can never be completely disregarded. One manufacturer (Carolina Medical Electronics, Inc.) however has taken the following three rather significant steps to minimize this danger: (1) construction of battery-powered flowmeter to eliminate need of the 110 volt 60 cycle wall current; (2) building an automatic probe cut-off which is actuated within 4 msec of the instant that any probe leakage occurs; and (3) isolation of the flowmeter output from chassis ground. These three innovations will be discussed in more detail in the following paragraphs.

Up until recently all electromagnetic flowmeters obtained their power from a 60 Hertz, 110 or 220 volt wall socket which has essentially zero impedance. These values of voltage and frequency have been found to present the optimum for alternating current stimulation of heart muscle. It would, therefore, be desirable to use a low capacitance transformer to isolate all existing operating room equipment from the alternating current lines. This would reduce the danger but would not guarantee against faulty connections between the transformer and the patient. The most satisfactory answer would be to power all equipment in operating rooms from low voltage DC (battery) source. We are now using a flowmeter that operates on rechargeable 27 volt battery. This flowmeter has the same stability and sensitivity as the AC operated models and will operate on one battery charge for about 4½ hours.

These instruments also tend to record any current produced by the patient or by ground loops. The signals generated in this manner could be as much as 1,000 times typical flow signal (i.e., the myocardial electrocardiogram (ECG) signal has 50 millivolt amplitude versus a flow signal which has only about 50 microvolts). The primary frequency of the ECG signals is around 30 Hertz and for the most part they are filtered out by driving the flowmeter probe at 270 Hertz. If flow is being recorded from sites very near or on the heart, such as the coronary artery where the ECG signals are very high, it may be necessary to use a 500 Hertz magnet drive to reduce or eliminate the ECG signal. Therefore, interference-free recordings from this equipment can be taken as good evidence that significant extraneous electric currents are not present in the patient, otherwise they would tend to be recorded and to obscure the desired information.

A feedback circuit has been designed and built into this flowmeter that detects situation when some of the power which goes to energize the probe is lost through an abnormal pathway such as a broken wire or faulty insulation. This circuit responds by shutting off power to the probe within less than 4 msec which from present evidence[10] should be fast enough to prevent fatal ventricular fibrillation. The flowmeter cannot be used again until the defect is corrected. The leakage current required to activate the circuit can be adjusted to less than 60 microamperes, which if this current flows into the patient, of course assumes worst-case total catastrophic failure in flowmeter probe or an equally unlikely wrong electrical connection. In actual probes these leakage currents, if present, will be contained inside the probe cable. The probe shut-off circuit will act as warning of an internal leakage in the probe or cable such as may occur if saline gets in through puncture in the covering or if the probe connector gets wet. The current actually flowing into the patient under these circumstances will be only small percentage of the total leakage current and most likely will be zero. Also, leakage such as this will normally be detected during the preliminary zero and gain checking procedure that is customary before the probe is put in place for flow recording.

Another built-in safety feature of the battery powered flowmeter with the automatic shut-off circuit is this circuit will be activated if one tries to

use the flowmeter while it is accidentally left on the AC power lines for battery recharging. It, therefore, becomes impossible to operate this flowmeter while it is connected to the line current. (This applies only to a flowmeter that operates only from a battery. We do not use for clinical work the flowmeters that have both battery and AC power supplies.)

The third safety feature that was built into these flowmeters was rewiring the output in such a way that the output is isolated from the flowmeter cabinet. The patient is then grounded only through the high impedance present between transformer windings where the maximum signal voltage is only 1 volt if the recording is full scale. In this situation the maximum stimulation that can reach the patient if an equipment ground connection should fail is 1 volt at 270 Hertz through a small capacitance as compared to AC operated equipment in which the maximum stimulation is about 60 volts at 60 Hertz through a much lower impedance. This significantly reduces the likelihood of ventricular fibrillation caused by current leakage into the flow probe from the flowmeter or from recording equipment connected to the flowmeter.[10]

In summary, catheterization can now produce an entire new set of information of value in view of the corrective surgery now being done on cardiovascular system. We have mentioned one example of such information. It also brings with it possibility of new dangers but these can be minimized or eliminated by being aware of them and by using modern electronic techniques. This paper has outlined some of the safety precautions that we employ in flow recording. Other diagnostic procedures may not lend themselves this readily to isolation from AC power lines but we feel that operating room safety will be increased in direct proportion to the extent to which leakage currents and ground loops can be reduced.

Robert F. Bond, Ph.D.
Adam B. Denison, Jr., M.D.
Department of Physiology
Bowman Gray School of Medicine of
Wake Forest University
Winston-Salem, N. C. 27103

REFERENCES

1. Burchell, H. B.: Electrocution hazards in the hospital or laboratory, Circulation 27:1015, 1963.
2. Whalen, R. E., and Starmer, C. F.: Electric shock hazards in clinical cardiology, Mod. Conc. Cardiovasc. Dis. 36:7, 1967.
3. Starmer, C. F., Whalen, R. E., and McIntosh, H. D.: Hazards of electric shock in cardiology, Amer. J. Cardiol. 14:537, 1964.
4. Whalen, R. E., Starmer, C. F., and McIntosh, H. D.: Electrical hazards associated with cardiac pacemaking, Ann. N. Y. Acad. Sci. 111:922, 1964.
5. Spencer, M. P., and Denison, A. B., Jr.: The square wave electromagnetic flowmeter, IRE Trans. Med. Elect. ME 6:220, 1959.
6. Field, R. K.: Would you put that probe on your sick grandmother? Electronic Engineer 28:35, 1969.
7. Ben-Zvi, S.: The lack of safety standards in medical instrumentation, Trans. N. Y. Acad. Sci. 31:731, 1969.
8. Bond, R. F., and Barefoot, C. A.: Evaluation of an electromagnetic catheter tip velocity-sensitive blood flow probe, J. Appl. Physiol. 23:403, 1967.
9. Curtis, H. J., and Cole, K. S.: Nerve Excitation and propagation, *in* Glasser, O., editor: Medical physics, Chicago, 1944, Yearbook Medical Publishers, Inc., pp. 798-805.
10. Dalziel, C. F., and Lee, W. R.: Lethal electric currents, IEEE Spectrum, February, 1969, pp. 44-50.

At the time this work was carried out, R. F. Bond was an Advanced Research Fellow of the American Heart Association.

Letters to the Editor

Evaluation of mitral stenosis

T the Editor

We are much interested in the work of Dr V L Oreshkov (AMER. HEART J 79 789 1970) because we were studying the same problem during the years 1962 to 1964. The results of our work were not submitted for publication and we now would like to report them in brief

The method pplied is essentially the same as that described by Dr Oreshkov and we will use the same symbols that he did. W studied 73 patients with pure mitral stenosis (MS) proved by catheterization 48 normal subjects served as controls

W found 2A-O in the 73 cases of MS to be poorly correlated (= −0 34) to the mean pulmonary capillary pressure (MPCP) The correlation of C 1 to the MPCP was little better (= 0.58) hich is of the same order as that found by Dr Oreshkov (= −0.45) who, however correlated C 1 to the diameter of the mitral orifice. The new index worked out was $\frac{C\text{-}1}{C\ E}$ in which E is the end of the isovolumetric contraction. the point t which the aortic valve opens. E can almost always be defined precisely on the ACG in MS (Fig. 3) should this not be possible, then the exact moment of opening of the aortic valve can be deduced from the carotid pulse tracing I our experience it is often difficult to localize accurately the point F; moreover in our series, the RFW was absent in one fourth of the cases of MS. The index $\frac{C\ 1}{C\ E}$ was chosen in order to eliminate the influence of the heart rate and other factors known to influence the contractility of the left ventricle (age, stroke volume, and the like). W expected the index to be positively correlated to the left trial pressure and MPCP Measurements ere made in duplicate independently by the tw of us on three successive contractions. I normal subjects the index was always less than 0.40. I the 73 cases of MS the correlation with the MPCP was very good (= 0.85 Fig. 1) I 69 cases the index was correlated to the surface of the orifice of the mitral valve as estimated at operation (Prof F Derom) the coefficient = −0.79 is of the same order as that found

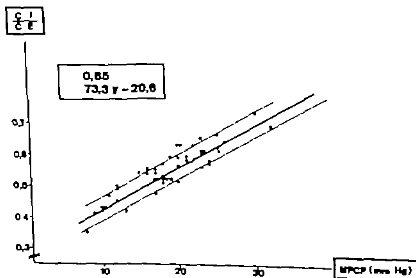


Fig. 1 Scatter diagram demonstrating the relationship of the $\frac{C\ 1}{C\text{-}E}$ index to the mean pulmonary capillary pressure (MPCP) in 73 cases of pure mitral stenosis. The correlation coefficient, the calculated regression line, and the standard deviation from the regression line are shown.

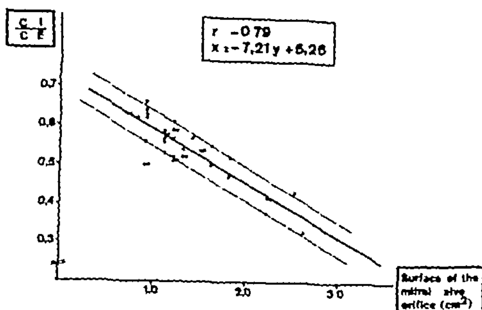
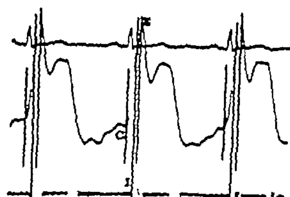


Fig 2 Scatter diagram illustrating the excellent correlation between $\frac{C\,I}{C\,E}$ and the surface of the mitral valve orifice in 69 cases of pure mitral stenosis The correlation coefficient the calculated regression line and the standard deviation from the regression line are shown.



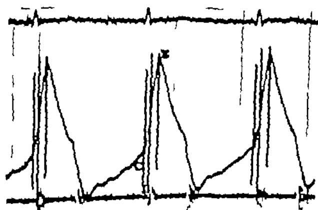


Fig 3 Above Based on the $\frac{C\,I}{C\,E}$ index (0 57) the surface of the mitral valve orifice was predicted to be 1.2 cm (±0.3 cm²) in this patient with pure MS. The surgeon found this estimation to be correct. Below After valvotomy the index is decreased to normal (0.33)

by Dr Oreshkov Whenever the index was equal to or less than 0 45 severe mitral stenosis (i.e., orifice surface less than 1.8 cm²) could be rejected (Fig 2)

After successful commissurotomy the index decreased to normal values (Fig 3) Prospective study during the last years has confirmed the validity of the method

Dr Frank Comhaire
Dr Philippe Uyttenhove
Department of Medicine
Akademisch Ziekenhuis,
State University Ghent Belgium

Reply

To the Editor

Drs. Comhaire and Uyttenhove use the C I interval (or initial phase of ventricular contraction) The advantage of this interval over the Q-I interval (or transformation time) in the diagnosis of mitral stenosis was demonstrated in a previous paper The results obtained by Drs. Comhaire and Uyttenhove offer new confirmation of this understanding

In order to eliminate the influence of heart rate and other factors known to influence the contractility of the ventricle, Drs. Comhaire and Uyttenhove use the $\frac{C\,I}{C\,E}$ ratio where the C E interval in their opinion corresponds to the isovolumetric contraction time They identify the E point (end of isovolumetric contraction and onset of ejection) with the peak of the systolic wave in the apexcardiogram (ACG) I have a remark to make about it. In my experience the peak of the systolic wave of the ACG usually coincides with the upstroke of

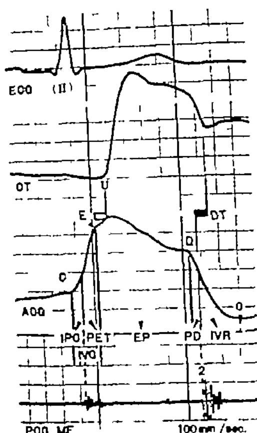


Fig. 1. IVC, Isovolumetric contraction (C-E interval). IPC, initial phase of contraction (C-1 interval). PET, pressure elevation time (1-E interval). C point, onset of ventricular contraction. E point, onset of ejection. U point, upstroke of the carotid tracing. 1, first heart sound. DT, delay time of the carotid pulse wave. ECG, electrocardiogram (Lead II). CT, carotid tracing. ACG, left ventricular apexcardiogram. PCG-MF, phonocardiogram—medium frequency (Oreshkov, V. I.: Jap. Heart J. 9:332, 1968).

the carotid tracing. Obviously the real E point precedes the onset of the carotid upstroke at an interval equal to the delay time of the carotid pulse wave.[6] (Fig. 1). Dallocchio and associates, and Tavel and associates, also found the E point to precede the peak of the systolic wave in the ACG. Therefore, the C-E interval as used by Drs. Combaire and Uyttenhove in most cases includes the delay time of the carotid pulse wave along with the isovolumetric contraction time.

The $\frac{C\text{-}1}{C\text{-}E}$ index suggested by Drs. Combaire and Uyttenhove correlates better with the mean pulmonary capillary pressure ($r = 0.85$) than does the C-1 interval ($r = 0.58$). Most probably that is due mainly to the following causes. The C-E interval as used by Drs. Combaire and Uyttenhove consists of three time intervals: the initial phase of ventricular contraction (C-1 interval), pressure elevation time (1-E interval, I mean the real E point) and the delay time of carotid pulse wave (E-U interval, U from upstroke of the carotid tracing) (Fig. 1). In mitral stenosis the C-1 interval is prolonged and the 1-E interval is shortened. Obviously the changes in 1-E interval increase the diagnostic reliability of the $\frac{C\text{-}1}{C\text{-}E}$ index in comparison with the reliability of the C-1 interval when it is used alone. In recent years I have used the $\frac{C\text{-}1}{1\text{-}E}$ index. In this way the changes in the duration of these two phases become more distinct and the delay time of the carotid pulse wave is eliminated. In normal subjects this index is usually smaller than 1 (mean 0.57 ± 0.39) while in mitral stenosis (34 patients) with a diameter of the mitral orifice from 2 to 15 mm. it varies between 0.82 and 9 (mean 2.56 ± 1.81, $t = 6.32$, $p < 0.001$).

My paper in the AMERICAN HEART JOURNAL was devoted to a new mechanocardiographic index in evaluating the severity of mitral stenosis. It represents the difference between the C-1 time interval and the duration of the rapid filling wave (O-F interval) on the ACG. Therefore, the $\frac{C\text{-}1}{C\text{-}E}$ index of Drs. Combaire and Uyttenhove is different and has its own significance. I included the O-F interval because it correlated with the diameter of the mitral orifice better than the C-1 interval did.

Vesselin I. Oreshkov, M.D.
Division of Cardiology
Higher Medical Institute
Sofia 31, Bulgaria

REFERENCES

1. Oreshkov, V. I.: Q-1 or C-1 interval in the diagnosis of mitral stenosis, Brit. Heart J. 29:778, 1967.
2. Oreshkov, V. I.: Apexcardiography. I. The normal apexcardiogram, Vitr. bol. (Sofia) 4:223, 1965.
3. Oreshkov, V. I.: Indirect measurement of isovolumetric contraction time on the basis of polygraphic tracing (apexcardiogram, carotid tracing, and phonocardiogram), Cardiologia (Basel) 47:315, 1965.
4. Dallocchio, M., Bricaud, H., Drouet, B., Bonavita, J. P., and Broustet, P.: Etude comparative d'un cardiogramme apexien et des tracés de pression intraventriculaire gauche, Arch. Mal. Coeur 58:1078, 1965.
5. Tavel, M. E., Campbell, R. W., Feigenbaum, H., and Steinmetz, E. F.: The apexcardiogram and its relationship to haemodynamic events within the left heart, Brit. Heart J. 27:829, 1965.
6. Oreshkov, V. I.: Diagnostic reliability of carotid tracing in mitral valve disease, Vitr. bol. 9:62, 1970.
7. Oreshkov, V. I.: A new mechanocardiographic index in evaluation of the severity of mitral stenosis. An apexcardiographic study, AMER. HEART J. 79:789, 1970.

Book reviews

ATLAS OF NUCLEAR MEDICINE, VOL. 2 LUNG AND HEART By Frank DeLand M D., and Henry N Wagner Jr M D Philadelphia 1970, W B Saunders Company 281 pages. Price $20 00.

This volume devoted to the lung and heart is primarily concerned with radioactive isotope scanning of the lungs. Very little is concerned with the heart itself Nevertheless, cardiologists will find this a very useful atlas since pulmonary disturbances are so common in association with heart disease The authors are concise in their presentation of scans of pulmonary embolism infections circulatory disease and pulmonary hypertension, as well as scans of the heart itself The discussions of equipment, technique artifacts, and normal variations are good The illustrations are clear and are based upon actual case records from Johns Hopkins Hospital Each illustration is supported by a clinical history prior diagnosis and the interpretation of the illustration with a final diagnosis. A scan and a roentgenogram are presented for practically all patients. In many instances there is a supporting diagnosis to clarify further the scan and its interpretation. This is a very good atlas. It can be used to learn to interpret scintigrams, as well as to show their value and limitations.

THE INNERVATION OF THE VERTEBRATE HEART Edited by Edwin F Hirsch M D Ph.D., Sc.D (Hon.) Springfield, Ill. 1970, Charles C Thomas, Publisher 208 pages. Price $16.50

This brief book on an extremely important and relatively little understood subject is written primarily by Dr Edwin F Hirsch with the assistance of 5 other co-authors. The presentation is primarily from the anatomic and morbid pathologic points of view Unfortunately very little normal or abnormal physiology or function is presented. There is a need, however for a book devoted to structural changes. The clinician needs to understand anatomic functional relationships to appreciate the application of normal and abnormal nervous structural states. Nevertheless this book is intended more for the comparative anatomist. The illustrations are numerous and excellent and the text, although brief is good. The animals discussed briefly include the hagfish, amphibians and aquatic vertebrates, feline animals, primates, and man. This is an interesting book devoted to an important and too often neglected aspect of the heart. There is a good bibliography Unfortunately the presentations are short and incomplete.

PROCEEDINGS OF THE FOURTH ASIAN PACIFIC CONGRESS OF CARDIOLOGY Sept. 1 to 7 1968 Jerusalem and Tel Aviv Israel. Edited by Marcel Eliakim, M D F.A.C.C., New York, 1969 Academic Press Inc. 515 pages. Price $24.50.

These proceedings of the Fourth Asian-Pacific Congress of Cardiology held in Tel Aviv Sept. 1 to 7 1968, describe very well the important aspects of cardiology of the present time The papers are clearly presented and the authors represent countries from all over the world. The Congress was concerned primarily with physiology and metabolism congenital defects, and ischemic heart disease. However papers were read on cardiomyopathy cardiac surgery and hypertension, as well as numerous other aspects of heart disease The Israelis did an excellent job in planning hosting, and conducting the session, and excellent work in producing this publication.

PATHOPHYSIOLOGY OF CONGENITAL HEART DISEASE. UCLA Forum in Medical Sciences, No. 10. Edited by Forest H Adams, H J C. Swan, and Victor E. Hall Los Angeles, 1970, University of California Press, 446 pages. Price $26.50.

This volume is a summary of the proceedings of a conference on pathophysiology of congenital heart disease held in Los Angeles during July 1967 Although this volume is rather slow in appearing, the discussions are still applicable today The volume consists of short papers on embryology normal physiology of the fetus and neonate, physiology of the abnormal neonate function of the myocytes, exercise physiology special physiologic problems, and bioengineering. As with all such proceedings, the volume consists of the paper presented and panel discussions conducted This is a good and useful publication which should interest all pediatricians, medical students, interns, and residents, as well as all cardiologists.

American Heart Journal

April 1971 Volume 81 Number 4

Editorial

Recent studies on cardiac hypertrophy

Barry L. Fanburg, M.D.
Boston, Mass.

A major postembryonic adaptation of the heart is the ability of this organ to respond to various stimuli by an increase in tissue mass. The mechanism by which this occurs and the composition and physiologic properties of the hypertrophied heart have been studied extensively. Three relatively contemporary developments have aided investigators of the heart in approaching this subject in more detail: (1) knowledge of the molecular biology of protein and nucleic acid synthesis in both mammalian tissues and bacteria has increased immensely, (2) information about the biochemistry and ultrastructure of skeletal muscle has advanced considerably and has paved the way for similar studies of heart muscle, and (3) physiologic studies first developed for isolated skeletal muscle now have been adapted to the heart.

The purpose of this communication is to review briefly and comment on the information that is now available on experimental cardiac hypertrophy in the laboratory animal. The data were obtained from many laboratories although only a partial bibliography is given. While it is likely that information gained from such studies ultimately will be useful in evaluating the clinical situation, such a relationship at the moment must be viewed as tentative. Furthermore, it should be kept in mind that information gained about the response of the heart to one type of stimulation for hypertrophy need not apply to the response to another type of stimulation.

Several methods have been used to produce cardiac hypertrophy in the experimental animal. Among these are constriction of the aorta or pulmonary artery, partial ligation of the renal artery after unilateral nephrectomy, treatment with thyroid hormone and related compounds, treatment with sympathomimetic drugs, production of anemia, creation of nutritional deficiency states, exposure to hypoxic conditions, production of myocardial ischemia, and exposure to stress.

The imposition of an increased afterload on the heart is frequently used for producing hypertrophy. With an increase in afterload, such as that caused by aortic constriction, one of the earliest *biochemical* changes that can be identified is an increase in RNA synthesis. Although the increase in total RNA or RNA concentration is insufficient to be measured until 1 to 2 days after imposing an increased work load, there is a stimulation of radioactive precursor labeling of RNA within the first few hours.[1-3] Several studies indicate that the early increase in RNA synthesis affects all types of cellular RNA (ribosomal, soluble, and messenger) to about the same extent. However, some evidence suggests that stimulation of messenger RNA precedes

From the New England Medical Center Hospitals, 171 Harrison Ave., and the Department of Medicine, Tufts University School of Medicine, Boston, Mass. 02111.
This investigation was supported by Grants 5T01 HE05924 and 5T01 HE08391 from the National Heart Institute, National Institutes of Health, United States Public Health Service.
Recipient of Research Career Development Award, National Institutes of Health.

that of the other types of RNA[4] confirmation of this finding awaits more specific means for identifying messenger RNA. The activity of RNA polymerase which catalyzes RNA synthesis from precursor nucleotides increases after an elevation in work load[4] but present information suggests that the stimulation of RNA labeling precedes, rather than follows, the increase in activity of the polymerase.

An increase in protein synthesis also occurs soon after an increase in cardiac work load. The question of whether the increase in RNA or the increase in protein synthesis comes first is not fully resolved. In vivo labeling experiments suggest that an increase in RNA precedes that of protein. In studies with the isolated heart it has been found that increased labeling of protein with radioactive amino acid occurs as early as 3 hours after an elevation in work load[4] In vivo studies have shown that increased labeling of protein with radioactive amino acids usually does not occur until 1 to 2 days after an increase in work load[7,8] The interpretation of many of these studies is hindered by the lack of information about the specific activity of precursor amino acid inside the cell.

There is an increase in ribosomes in the hypertrophying heart and these provide additional sites for protein synthesis. It appears that there is no increase in protein synthesis per ribosome when this is determined on the basis of RNA content.[9] Furthermore there is no evidence for stimulation of soluble factors in cell sap to account for increased protein synthesis.

Measurements of DNA indicate for the most part that the total quantity of heart DNA increases with hypertrophy pari passu with the increase in tissue mass hence DNA concentration either remains unchanged or decreases with hypertrophy. There has been long-standing uncertainty as to whether the increase in tissue mass in the hypertrophied heart represents an increase in the number of heart muscle cells or an increase in muscle cell size. Recently it has been demonstrated by radioautography that new DNA synthesis takes place during cardiac hypertrophy almost entirely in interstitial as opposed to muscle cells.[10,11] There probably has been insufficient appreciation that interstitial cells outnumber muscle cells by about 3 to 1 in the heart.

The majority of studies on changes in nucleic acid and protein synthesis in hearts subjected to an increased work load have been done in the intact animal. However there have been some studies with the isolated perfused heart.[4] With the isolated system careful regulation of mechanical parameters may be obtained. Hence it would appear that such a system could offer many advantages for a detailed study of the influence of heart mechanics on nucleic acid and protein synthesis. For example it might be possible to determine if any particular parameter of contraction plays a predominant role in the syntheses of these substances and if specific modifications in contraction alter their production. Such studies have not yet been reported.

There are several inherent difficulties in this type of an evaluation. First, the muscle is in an abnormal situation in the isolated state. Second any bacterial contamination may cause a considerable problem since bacteria incorporate radioactive precursor much more rapidly than mammalian tissue and small numbers of bacteria which may be insensitive to antibiotics, can cause a marked alteration in labeling of extracted nucleic acids.[12] Labeling of bacterial RNA extracted along with that of the mammalian tissue would be undetected unless a more specific analysis of the RNA such as by density gradient separation were performed. Another consideration is that alterations in the mechanics of contraction may alter membrane transport of radioactive precursor and unless the intracellular precursor specific activity is taken into account labeling of nucleic acids or proteins may only reflect changes in transport of the labelled precursors.

There have been several studies to evaluate possible changes in cellular organelles and chemical constituents of the hypertrophied heart. Although the number of muscle cells does not seem to be increased the number of myofibrils per muscle cell is increased.[13] There does not appear to be an alteration in the geometry of thick or thin filaments, and the electron microscopic appearance of myosin is unchanged.[14] Dis-

tention of the sarcotubular system has been reported and various changes in the appearance of mitochondria have been described.[15]

Although the data have been somewhat variable there is at present no compelling reason to believe that there is a defect in mitochondrial oxidative phosphorylation or ATP availability in the hypertrophied heart. The calcium transporting activity of the isolated sarcoplasmic reticulum has not been studied in hypertrophy. Such a study would be of interest although small changes may be difficult to detect.

Several biochemical alterations have been found in the hypertrophied heart. There is often an increase in collagen but the extent of this change appears to be related to the method for inducing hypertrophy. For example constriction of the aorta results in an increase in both content and concentration of collagen while there may be little change in content and a decrease in concentration of collagen in hypertrophy produced by sideropenic anemia.[4] The concentration of catecholamines has been found to be depressed in hypertrophy. Amino acid concentration has been found to be increased.[15] Although there is little, if any available information on glucose and fatty acid transport or metabolism in the hypertrophied heart, studies with the isolated perfused heart have shown glucose and fatty acid uptake and utilization to be work-dependent.[13,29]

Several studies have related hormonal function to cardiac hypertrophy. It appears that growth hormone is not a requirement for muscle hypertrophy produced by an increase in work load.[31-33] The lesser extent of induced heart growth in the hypophysectomized as compared to the normal animal appears to be primarily a function of hemodynamic and mechanical differences. It has been suggested however that thyroid hormone may participate in heart growth by its direct action on protein synthesis.[34] A defect in protein synthesis by heart ribosomes has been demonstrated in the diabetic animal[35] but there is no information about the effect of diabetes on the response of the heart to a stimulus for hypertrophy.

Studies on the mechanics of the hypertrophied heart in the intact animal have been hampered by difficulties in the control of variables such as initial muscle length and differences in muscle mass between hypertrophied and control hearts. The isolated muscle preparation in which these variables can be readily controlled, has been useful in studying the performance of hypertrophied muscle. Investigations to date suggest that there is a decrease in the maximum velocity of contraction of hypertrophied muscle while the isometric developed tension per unit of cross-sectional area remains unchanged.[36,37] The decrease in maximum velocity has been interpreted as evidence of a depressed contractile state, although alternate explanations are possible depending upon the analogue model of muscle employed to derive contractile element velocities. Prolongation of the active state may compensate for the decrease in contractility thus enabling the hypertrophied heart to sustain a normal stress. The basis for the depression of contractility in hypertrophied heart muscle has not been established. It has been proposed that the reduced contractility is related to a decrease in cardiac myofibrillar ATPase activity. Further studies on isolated contractile proteins may be useful. The relation of function to structural and biochemical alterations is uncertain at present.

It appears that the development of hypertrophy is a method of temporary compensation for an increased cardiac work load. It is quite possible that any increase in work load, regardless of its duration sets in motion a sequence of biochemical alterations of the muscle cell. Whether the initial transmission of a mechanical to a biochemical change occurs at the cell membrane or in the interior of the cell is, at the moment, unknown. If the increased work load is not sustained the biochemical alterations may be readily reversible. With maintenance of an increased work load there are alterations in the ultrastructure, in the organelles, and in the biochemical composition of the muscle cell. The extent of reversibility of these changes is not known. As knowledge about these alterations increases, we may gain a clearer understanding of the process by which the heart becomes incompetent and heart failure ensues.

REFERENCES

1. Fanburg B L Experimental cardiac hypertrophy New Eng J Med 282:723 1970
2. Fanburg B L and Posner B I Ribonucleic acid synthesis in experimental cardiac hypertrophy in rats. I Characterization and kinetics of labeling Circ. Res. 23:123 1968.
3. Koide T and Rabinowitz M Biochemical correlates of cardiac hypertrophy II Increased rate of RNA synthesis in experimental cardiac hypertrophy in the rat Circ Res, 21:9 1969
4. Schreiber S S Oratz M., Evans, C Silver E. nd Rothschild M A. Effect of acute over load on cardiac muscle mRNA Amer J Physiol 215:1250 1968.
5. Nair K. G Cutilletta A F., Zak R., Koide T and Rabinowitz M Biochem cal correlates of cardiac hypertrophy I Experimental model Changes in heart weight, RNA content, and nuclear RNA polymerase activity Circ. Res. 23:451 1968.
6. Schreiber S. S Oratz M and Rothschild M A. Protein synthesis in the overloaded mammalian heart Amer J Physiol 211:314 1966
7. Meerson F Z Compensatory hyperfunction of the heart and cardiac insufficiency Circ Res. 10:250 1962
8. Gudbjarnason S. Telerman, M and Bing R J Protein metabolism in cardiac hypertrophy and heart failure Amer J Physiol 206:294 1964
9. Moroz L. Protein synthetic activity of heart microsomes and ribosomes during left ventricular hypertrophy in rabbits, Circ Res 21:449 1967
10. Grove D Nair K G and Zak R Biochemical correlates of cardiac hypertrophy III Changes in DNA content The relative contributions of polyploidy and mitotic activity Circ. Res. 25:463 1969
11. Morkin, E. and Ashford T P Myocardial DNA synthesis in experimental cardiac hypertrophy Amer J Physiol 215:1409 1968
12. Fanburg B I and Posner B. I Labeling of RNA in the perfused heart The problem of bacterial contamination Biochim. Biophys. Acta 182:577 1969
13. Richter G. W and Kellner A. Hypertrophy of the human heart at the level of fine structure An analysis nd two postulates, J Cell Biol 18 195 1963
14. Carney J A and Brown A L The morphology of myosin in cardiac hypertrophy Lab. Invest 16:36, 1967
15. Meessen H Ultrastructure of the myocardium its significance in myocardial disease Amer J Cardiol 22:319 1968.
16. Bartsova D Chvapil M., Korecky B. Poupa, O Rakusan K Turek Z., and Vizek, M The growth of the muscular and collagenous parts of the rat heart in various forms of cardiomegaly J Physiol 200:285 1969
17. Chidsey C. A. Kaiser G A., Sonnenblick, E. H Spann, J F Jr and Braunwald E. Cardiac norepinephrine stores in experimental heart failure in the dog J Clin. Invest. 43:2386, 1964
18. Wannemacher R W Jr and McCoy J R. Regulation of protein synthesis in the ventricular myocardium of hypertrophic heart Amer J Physiol 216:781 1969
19. Neely J R Liebermeister H and Morgan, H E. Effect of pressure development on membrane transport of glucose in isolated rat heart Amer J Physiol 212:815 1967
20. Neely J R. Bowman, R. H and Morgan, H E. Effects of ventricular pressure development and palmitate on glucose transport, Amer J Physiol 216:804 1969
21. Morkin, E Garrett J C. and Fishman, A P Effects of actinomycin D and hypophysectomy on development of myocardial hypertrophy in the rat Amer J Physiol. 11:6, 1968.
22. Lipana J G and Fanburg B L. Heart growth in response to aortic constriction in the hypophysectomized rat Amer J Physiol. 218:641 1970.
23. Goldberg A. L. Work-induced growth of skeletal muscle in normal and hypophysectomized rats, Amer J Physiol. 213 1193 1967
24. Cohen J Aroesty J M and Rosenfeld, M G Determinants of thyroxine-induced cardiac hypertrophy in mice Circ Res. 18:388 1966
25. Wool I G Stirewalt W S and Moyer A N Effect of diabetes and insulin on nucleic acid metabolism of heart muscle Amer J Physiol 214:825 1968
26. Spann J F Jr Buccino, R A Sonnenblick, E. H and Braunwald E. Contractile state of cardiac muscle obtained from cats with experimentally produced ventricular hypertrophy and heart failure Circ. Res. 21:341 1967
27. Bing O H L Matsushita S Fanburg B L. and Levine H. J Myocardial contractility during left ventricular hypertrophy Circulation 40 (III) 46, 1969 (Abst.)

Clinical communications

Reassessment of parasystole

Yoshio Watanabe, M.D.
Philadelphia, Pa.

During the past decade significant progress has been made in our understanding of cardiac arrhythmias, particularly through numerous clinical and experimental studies utilizing electrophysiological as well as pharmacological approaches. Resultant emergence of newer concepts in the genesis of cardiac arrhythmias has been extensively reviewed by several authors. Despite such progress the precise mechanisms of many rhythm disturbances still remain unknown. For instance, the genesis of a coupled premature systole—one of the simplest and most common forms of abnormal rhythms—has not been identified either as the result of a new impulse formation or re-entry of one and the same impulse which caused the preceding depolarization of the cardiac muscle.

On the other hand, there appears to be general agreement that parasystole is an expression of regular impulse formation in an ectopic focus outside the sinoatrial node, this focus being independent of and protected from impulses which are predominantly controlling the cardiac rhythm. The mechanism for such independent impulse formation most likely is automaticity in the form of slow diastolic depolarization of the cell membrane in specialized fibers of the heart. However, occasional observations of the transition between a parasystolic rhythm and "coupled extrasystoles" in a given patient may provide us with some insight into the genesis of both types of arrhythmias. One of the possibilities in explaining the apparent link between these two rhythm disturbances has been presented by Schamroth and Marriott. Furthermore, several other phenomena associated with parasystole still await more studies. These include the mechanism of protection of the parasystolic pacemaker, possible sites of impulse formation, and the mechanisms of intermittence as well as exit block.

In this communication an attempt will be made to answer these and other questions by clinical observations, although more extensive experimental work is definitely needed. The present study is based on the analysis of 58 electrocardiograms from 21 patients where strict application of the accepted criteria for parasystole indicated the presence of this rhythm. All the tracings were obtained from the files in the Heart Station of the Hahnemann Medical College and Hospital. Time intervals are expressed in hundredths of a second unless otherwise specified.

Results

Observations on several interesting electrocardiograms are presented first, and will be followed by analyses of the data from the entire group. Patients will be referred to by the initials.

From the Division of Cardiology, Department of Medicine and Department of Physiology and Biophysics, Hahnemann Medical College, Philadelphia, Pa.
Received for publication April 22, 1970.
Reprint requests to: Yoshio Watanabe, M.D., Hahnemann Medical College, 230 North Broad Street, Philadelphia, Pa. 19102.

REFERENCES

1 Fanburg B L. Experimental cardiac hypertrophy New Eng J Med 28_:723 1970
2. Fanburg B L and Posner B I Ribonucleic acid synthesis in experimental cardiac hypertrophy in rats. I Characterization and kinetics of labeling Circ. Res. 23:123 1968
3 Koide T and Rabinowitz M Biochemical correlates of cardiac hypertrophy II Increased rate of RNA synthesis in experimental cardiac hypertrophy in the rat Circ. Res. 24:9 1969
4 Schreiber S S Oratz M Evans, C Silver E. and Rothschild M A. Effect of acute overload on cardiac muscle mRNA Amer J Physiol 215:1250 1968
5 Nair K. C Cutilletta A F Zak R Koide T and Rabinowitz M Biochemical correlates of cardiac hypertrophy I Experimental model Changes in heart weight RNA content and nuclear RNA polymerase activity Circ. Res. _3:151 1968
6. Schreiber S. S. Oratz, M and Rothschild M A. Protein synthesis in the overloaded mammalian heart Amer J Physiol 211:314 1966
7 Meerson, F Z Compensatory hyperfunction of the heart and cardiac insufficiency Circ Res. 10:250 1962
8 Gudbjarnason S. Telerman M and Bing R J Protein metabolism in cardiac hypertrophy and heart failure Amer J Physiol 206:294 1964
9 Moroz, L. Protein synthetic activity of heart microsomes and ribosomes during left ventricular hypertrophy in rabbits, Circ Res. 21:449 1967
10. Grove D Nair K. G and Zak, R Biochemical correlates of cardiac hypertrophy III Changes in DNA content The relative contribution of polyploidy and mitotic activity Circ. Res. 25 463 1969
11 Morkin, E and Ashford T P Myocardial DNA synthesis in experimental cardiac hypertrophy Amer J Physiol 215:1409 1968
12 Fanburg B L. and Posner B I Labeling of RNA in the perfused heart The problem of bacterial contamination, Biochi Biophys. Acta 182:577 1969
13 Richter G W and Kellner A Hypertrophy of the human heart at the level of fine structure An analysis and two postulates, J Cell Biol 18:195 1963
14 Carney J A and Brown, A. L. The morphology of myosin in cardiac hypertrophy Lab. Invest. 16:36 1967
15 Messen H Ultrastructure of the myocardium, its significance in myocardial disease, Amer J Cardiol 22:319 1968.
16. Bartková D., Chvapil M Korecky B Poupa, O Rakusan K. Turek Z and Vizek, M The growth of the muscular and collagenous parts of the rat heart in various forms of cardiomegaly J Physiol 200:285 1969
17 Chidsey C A Kaiser G A. Sonnenblick, E. H Spann J F Jr and Braunwald, E. Cardiac norepinephrine stores in experimental heart failure in the dog J Clin. Invest. 43:_386, 1964
18 Wannemacher R. W Jr and McCoy J R. Regulation of protein synthesis in the ventricular myocardium of hypertrophic hearts, Amer J Physiol 216:781 1969
19 Neely J R Liebermeister H and Morgan, H E. Effect of pressure development on membrane transport of glucose in isolated rat heart Amer J Physiol 21 :815 1967
20. Neely J R Bowman, R. H and Morgan, H E. Effects of ventricular pressure development and palmitate on glucose transport, Amer J Physiol. 216:801 1969
21 Morkin E. Garrett J C. and Fishman, A. P Effects of actinomycin D and hypophysectomy on development of myocardial hypertrophy in the rat Amer J Physiol. 11:6 1968.
22 Lipana J G and Fanburg B L. Heart growth in response to aortic constriction in the hypophysectomized rat Amer J Physiol. 218:611 1970
23 Goldberg A. L. Work induced growth of skeletal muscle in normal and hypophysectomized rats, Amer J Physiol. _13:1193 1967
24 Cohen J Arcestry J M and Rosenfeld M G Determinants of thyroxine-induced cardiac hypertrophy in mice Circ. Res. 18:388, 1966.
25 Wool I G Stirewalt W S. and Moyer A N Effect of diabetes and insulin on nucleic acid metabolism of heart muscle Amer J Physiol. 214:825 1968
26 Spann J F Jr Buccino, R. A. Sonnenblick, E. H and Braunwald E Contractile state of cardiac muscle obtained from cats with experimentally produced ventricular hypertrophy and heart failure Circ. Res. 21:341 1967
27 Bing O H. L. Matsushita S. Fanburg B L. and Levine H J Myocardial contractility during left ventricular hypertrophy Circulation 40 (III) 46, 1969 (Abst.)

Clinical communications

Reassessment of parasystole

Yoshio Watanabe, M.D.
Philadelphia, Pa.

During the past decade significant progress has been made in our understanding of cardiac arrhythmias, particularly through numerous clinical and experimental studies utilizing electrophysiological as well as pharmacological approaches. Resultant emergence of newer concepts in the genesis of cardiac arrhythmias has been extensively reviewed by several authors. Despite such progress the precise mechanisms of many rhythm disturbances still remain unknown. For instance, the genesis of a coupled premature systole—one of the simplest and most common forms of abnormal rhythms—has not been identified either as the result of a new impulse formation or re-entry of one and the same impulse which caused the preceding depolarization of the cardiac muscle.

On the other hand, there appears to be general agreement that parasystole is an expression of regular impulse formation in an ectopic focus outside the sinoatrial node, this focus being independent of and protected from impulses which are predominantly controlling the cardiac rhythm. The mechanism for such independent impulse formation most likely is automaticity in the form of slow diastolic depolarization of the cell membrane in specialized fibers of the heart. However, occasional observations of the transition between a parasystolic rhythm and coupled extrasystoles in a given patient may provide us with some insight into the genesis of both types of arrhythmias. One of the possibilities in explaining the apparent link between these two rhythm disturbances has been presented by Schamroth and Marriott. Furthermore, several other phenomena associated with parasystole still await more studies. These include the mechanism of protection of the parasystolic pacemaker, possible sites of impulse formation, and the mechanisms of intermittence as well as exit block.

In this communication, an attempt will be made to answer these and other questions by clinical observations, although more extensive experimental work is definitely needed. The present study is based on the analysis of 58 electrocardiograms from 21 patients where strict application of the accepted criteria for parasystole indicated the presence of this rhythm. All the tracings were obtained from the files in the Heart Station of the Hahnemann Medical College and Hospital. Time intervals are expressed in hundredths of a second unless otherwise specified.

Results

Observations on several interesting electrocardiograms are presented first, and will be followed by analyses of the data from the entire group. Patients will be referred to by the initials.

From the Division of Cardiology, Department of Medicine, and Department of Physiology and Biophysics, Hahnemann Medical College, Philadelphia, Pa.
Received for publication April 22, 1978.
Reprint requests to: Yoshio Watanabe, M.D., Hahnemann Medical College, 230 North Broad Street, Philadelphia, Pa. 19102.

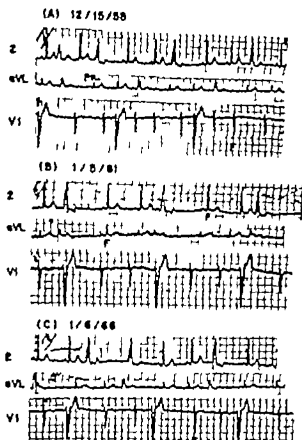


Fig. 1 Patient B H Parasystolic activity of over 7 years duration The electrocardiogram is normal except for the arrhythmia F fusion beat. Detailed discussion in text

Individual observations

PATIENT B H A total of six electrocardiograms were obtained on this patient three during the month of December 1958 one in January 1961 and two in January 1966. Three of the six tracings are reproduced in Fig 1 each showing Leads II, aVL, and V In (A) taken Dec. 15 1958 sinus arrhythmia is present which is interrupted by frequent premature systoles showing a longer QRS duration with a wide variation of the coupling interval The shortest interectopic interval measures 118 in seen between the second and fourth QRS in Lead II while the longer interectopic intervals (e g between beats 4 and 7 and beats 7 and 10 in the same lead) are multiples of this basic interval. Beat 10 in Lead V_1 results from fusion of the dominant and parasystolic impulses A total of 41 parasystolic beats were found in the entire twelve lead with coupling intervals ranging from 31 to 75 On one occasion two consecutive parasystolic beat appeared without an intervening sinus beat revealing a pure parasystolic interval of 118. The parasystolic cycle length including single or the shortest ones and those calculated from longer interectopic interval had a narrow range of 116 to 120 with a mean and standard error of 118.4 ± 0 29 This interval corresponds to a rate of 51 beats per minute Two other electrocardiograms recorded on the following day and a week later showed the same parasystolic mechanism operative with mean cycle lengths of 119 3 and 120 7 respectively despite marked variations in the sinus rate on these two days (between 60 and 125 beats per minute)

In both parts (B) and (C) of Fig 1 taken Jan. 5 1961 and Jan 6 1966 respectively parasystolic

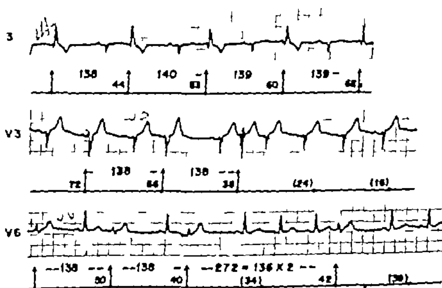


Fig 2 Patient J D Parasystole showing periods of bigeminy with both progressive prolongation and shortening of coupling intervals. Closed circles in the diagram and upward arrows show the time of ectopic discharge and successful propagation, respectively The numbers in small letters represent coupling intervals while those in larger letters show parasystolic cycle lengths. Numbers in parentheses indicate estimated coupling intervals of nonpropagated parasystolic impulses.

ventricular beats are agai easily identified th almost identical QRS configuration as seen i (*A*). The mean parasystolic cycle lengths on these tw occasions ere 131.8 nd 129.4 showing somewhat slower rate of impulse formation (approximately 46 beats per minut). Nevertheless, one can be reasonably certai that, in this instance, parasystolic mechanism remained active for t least seven years. T our knowledge this is the longest record of continuous parasystolic activity hich ppeared in the literature. It is i teresting to note that the electrocardiograms are considered normal except for the arrhythmia. The relatively stable rate of this ectopic rhythm during this long period of observation should also be stressed.

Another patient with persistent parasystolic activity as observed (Patient A. 31 O) in the present series. All three electrocardiograms recorded on this patient over period of t years and nine months (January 1966 April, 1968 and October 1968) showed the same parasystolic focus operative, ith mean cycle lengths of 118.9 111.0 and 118.2, respectively. Examples of exit block ere seen on several occasions. The electrocardiograms ere considered normal except for the arrhythmia, finding similar to that in Patient B. H

ATIENT J. D. This patient illustrates that parasystolic rhythm can cause both progressive prolongation and shortening of the coupling intervals in series of ventricular premature systoles showing bigeminal pattern (Fig 2) I Lead III five ventricular premature systoles are seen with alternating sinus beats. The coupling interval of the first premature systole cannot be precisely determined only the terminal portion of the QRS of the preceding si us beat is seen t the beginning of the strip. It is roughly estimated as 44. The coupli g intervals of the remaining four extrasystoles show progressive prolongation, measuring 44 53 60 and 62, respectively. Thus the P s ves gradually emerge i front of the QRS of these beat toward the end of this strip. I contrast, the coupling intervals of three premature systoles in V show gradual shortening from 72 t 56 and 38. Finally the subsequent discharge of the parasystolic focus probably occurred at coupling intervals of 24 nd 16 but f iled t be propagated. The bottom record in Fig. 2 (Lead V₄) show initial shortening of the coupling interval from 50 t 40 and one parasystolic beat fails to be propagated t n estimated coupl g interval of 34. The next parasystolic beat emerges with longer coupling interval of 42.

I this case, the interectopic intervals remain ithin narrow range of 136 to 140 (mean and tandard error 138.7 ± 0.23) while there is considerable degree of sinus arrhythmia with the cycle length fluctuating bet een 66 and 76. This is strong argument for the presence of an independent, parasystolic focus and against the so-called coupled extrasystoles with some variation in the coupling terval. Under these circumstances, two sinus tervals almost corresponding to one parasystolic cycle length could result in a bigeminal rhythm, ith either progressiv prolongation or shortening

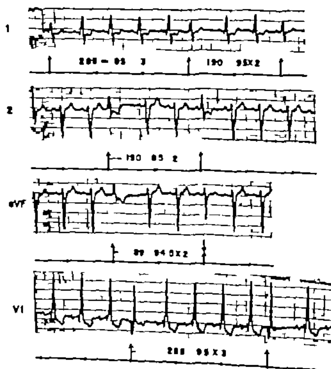


Fig. 3 Patient E. R Calculation of parasystolic cycle length from interectopic intervals. Diagrams similar to those in Fig. 2. Two arrows pointing to each other in VF represent ventricular fusion.

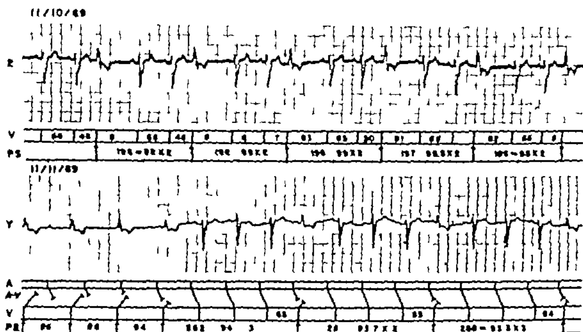


Fig 4 Patient F R Possible example of a parasystolic rhythm causing fixed coupling interval. A time of atrial activation A-V atrioventricular conduction V time of ventricular excitation with R R intervals P S parasystolic discharge with interectopic intervals. See text for discussion

of the coupling intervals Demonstration of both shortening and prolongation of the coupling intervals of the parasystolic beats in the same patient as a result of sinus arrhythmia is rare and appeared only in one early report

PATIENT F R The electrocardiogram reproduced in Fig 3 was recorded on this patient on Nov 9 1969 The basic rhythm is a sinus tachycardia which is interrupted by frequent premature systoles. The coupling interval of these premature systoles showed a wide variation between 38 and 59 with examples of ventricular fusion (e g beat 7 in aV_F) Two sets of interectopic intervals were found in the entire tracing Relatively shorter ones measured 188 to 192 (average 190) while longer ones measured 282 to 288 (average 285) By finding the greatest common divisor of 190 and 285 a parasystolic cycle length of 95 (94 9 ± 0.24) can be identified, although a single parasystolic interval was not observed

On the following day a long strip of Lead II was obtained a part of which is reproduced in Fig 4 top. In approximately three minutes, 72 premature systoles were recorded with a premature systole always following upon two sinus beats. The coupling intervals showed only slight variation from 45 to 51 and ventricular fusion was not observed. The interectopic intervals are quite constant as seen in this figure. This is expected when coupled premature systoles appear after a given number of sinus beats in the presence of regular sinus rhythm and a fixed coupling interval. Accordingly parasystole cannot be invoked simply on this basis. In this instance however the interectopic intervals measured 196 to 200, corresponding closely to the shorter interectopic intervals (190) seen on the previous day This interval corresponds also to three sinus cycles, which remain quite stable. It seems logical to invoke the same parasystolic rhythm although operating at a slightly slower rate, as the mechanism of trigeminal pattern with apparently fixed coupling (see diagram below the tracing)

Further argument for this explanation may be developed from the observations shown at the bottom of Fig 4 recorded on the following day In this record of orthogonal Lead Y the first four beats show a QRS contour similar to the parasystolic beats in Lead II (Fig 3 Fig 4 top) and bear no fixed relationship to the P waves. Their cycle length varies between 94 and 96 a value identical to the parasystolic interval seen in Fig 3 Hence transient control of the ventricles by pure parasystolic rhythm is indicated. The series of these four beats then followed by regular alternation of three sinus beats and one premature systole Both the sinus cycle and the coupling intervals of these premature systoles remain constant. The interval between the last of the four parasystolic beat and the first premature systole as well as the following interectopic intervals, measure almost exactly three times the parasystolic cycle length Hence persistent parasystolic activity with successful propagation of every third impulse seems a more likely explanation than regular occurrence of coupled premature systoles following abrupt termination of parasystolic rhythm. Two additional tracings taken four and six days later revealed the same parasystolic focus still active although the cycle length was somewhat prolonged to 108 and 116 respectively In one of these tracings, a sequence of events which is the reverse of that seen in Fig 4 bottom was observed i.e. the transition from trigeminal pattern with more or less fixed coupling to a series of three consecutive parasystolic beats. Here again the interval between the last premature systole of trigeminal rhythm and the first parasystolic beat

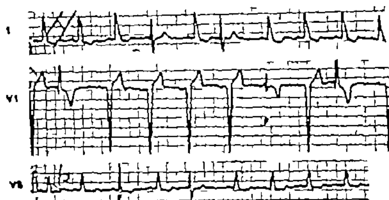


Fig. 5 Patient C. B Parasystolic rhythm i the presence of left bundle branch system block. Parasystolic beats show right bundle branch block configuration, with narrowing of QRS in fusion beats.

measured tw parasystolic cycles. Thus, this case may well be an example of fixed coupling intervals caused by simple mathematical relationship between the sinus and the parasystolic intervals.

PATIENT C. B. Of the numerous electrocardiograms taken on this patient, six tracings demonstrated the presence of parasystole for period of three months. Fig. 5 illustrates the relationship between intraventricular conduction disturbance nd possible location of the parasystolic focus. The sinus beats show changes characteristic of left bundle branch system block. I contrast, the parasystolic beats show the pattern of right bundle branch sy tem block, suggesting location of the parasystolic focus within or close to the left bundle branch system here conduction delay is present. If this is true, discharge of the parasystolic focus t time hen sinus impulse is just spreading through the intact right bundle branch sy stem would result a more normal, synchronous activation of the entir ventricles and consequently narrower QRS. This is clearly demonstrated in the presence of fusion beats, g. beat 7 in V and beat 5 in V

I this case, five of the six electrocardiograms showing parasystole ere taken ithin three- eek period. These five tracings revealed the parasystolic cycle length to be remarkably stable ith nar row range of 146 to 152 (mean and standard error = 148.4 ± 0.30). On the other hand, the sixth tracing hich was recorded tw months later showed several interesting features to be discussed in detail (Fig. 6). The four leads reproduced t the top (I 2, 3 and V_1) are so aligned that the same temporal relationships of series of beats are readily recognized. At the extreme left are two sinus beats (only the second one is seen in II and V_1) th cycle length of 80. The P R interval measures 24, showing first degree A V block. The next sinus P w is followed by narrower QRS (particularly in III V_1) ith evidence of right bundle branch system delay as ell as shorter P R interval. Hence, ventricular fusion is indicated. The following P wave occurs after significantly longer interval of 116, ith distinct change configuration. This suggests either shift of pacemaker or an ltered spread of excitation ithin the trial tissue. The next complex (beat 5) show similar characteristics as in beat 4 and occurs after a interval of 108. Beat 6 occurs prematurely with coupling interval of 64 and shows a right bundle branch block configuration. This is clearly paras tolic beat. The interectopic interval bet een the preceding fusion beat (beat 3) and this premature systole measures 290 nd corresponds t t parasystolic cycle lengths (see diagram). A nonconducted P wave is seen on the upstroke of the T wave of this beat after a P P interval of 97 to 104.

The most interesting beat is the following beat hich is numbered 7. Here, a QRS ppears after an interval of between 118 and 125 in these four leads, ith different degrees of P R shortening. The P ave is entirely hidden in the QRS in Lead II. This QRS has contour similar to the preceding paras tolic beat except in Lead II where it more closely resembles the fusion beat (beat 3). Therefore one might assume that this beat as caused by the next parasystolic discharge, showing sudden acceleration for some nknown reason. However this explanation is challenged because of the following findings.

I beat 8, the P e occurs after shorter P-P interval of 86 to 88, and shows configuration identical to that in beats 1 and 2. The QRS also is similar to that in beat . Hence, this beat is considered sinus be t. I Leads II and aV premature QRS complex follows this sinus beat t a coupling interval of 60 and 64, respectively. The configuration resembles other parasystolic beats. A sinus P ave occurring with still shorter P P interval of 76 distorts the initial part of the QRS in Lead II. This beat must then be interpreted as another parasystolic beat. If one measures the interval bet een beat 6 and this beat (numbered 9) it is found to be 290, agai corresponding to t ice the parasystolic cycle length. This implies that, if beat 7 ere parasystolic one caused by sudden acceleration of the focus (from an interval of 145 to 118 or 125) the rhythm must have slowed again to a cycle length of 172 or 165

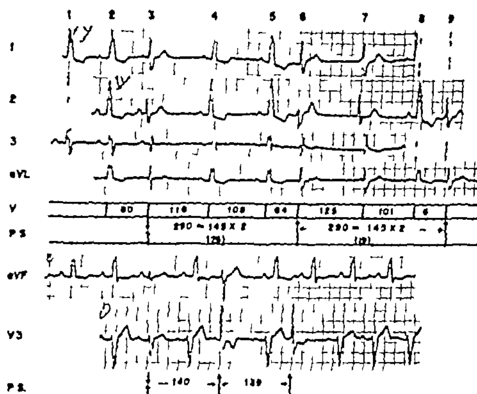


Fig 6 Patient C. B Complex arrhythmia caused by parasystole and possible escape beats originating from the region of parasystolic focus Detailed discussion in text

Table I Summary of cases

Patient		Number of ECG	Sinus beats		Parasystolic beats	
No	Name		Range of cycle length	Intraventricular conduction	Mean cycle length	Intraventricular conduction
1	R A.	2	62 75	LAH (−50°)	121 1	LPH? (+105°)
2	L. B	3	49-75		143 6	RBBB
3	J B	1	(AF)		60.6	LBBB (LAH)†
4	C. B	6	69-112	LBBB	147 4	RBBB
5	M C.	2	69-81		122.5	LBBB
6	N D	5	52-61	LAH (−45)	152 4	LPH? (+130°)
7	J D	3	60-83		139 7	RBBB
8	B H	5	48-101		124 1	LBBB
9	D H	2	78-86	RBBB+LAH	142.4	LBBB (LAH)†
10	M J	2	62 73	LAH (−45°)	131 6	LAH (−47°)
11	I K.	6	75-88		225 0	RBBB
12	H K	1	61 75	LAH (−47°)	276.4	LAH (−77°)
13	I M	1	68-71		92 6	RBBB+LAH
14	J M	6	61 100	LBBB	125 1	RBBB
15	A M O	3	47 76		115 1	LAH
16	B P	1	56-84		173.5	RBBB
17	E. R.	4	58-72	RBBB+LAH	101 1	RBBB
18	C S.	1	78-116		131 4	RBBB
19	G S.	2	75-113		222 1	RBBB+LAH
20	R. S.	1	84-92		145 9	LAH
21	F W	1	(AF)		157 6	RBBB

Abbreviations: AF = Atrial fibrillation; LBBB = left bundle branch block; RBBB = right bundle branch block; LAH = left anterior hemiblock LPH = left posterior hemiblock.

*Mean QRS axis.

†Left bundle branch block with major delay in the anterior division of the left bundle.

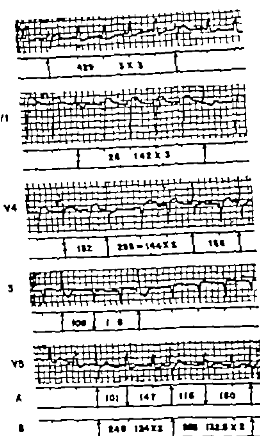


Fig 7 Patient J M Example of intermittent parasystole with wide variation of cycle length. Diagrams below V show likely mechanism of intermittence (*A*) and an alternative explanation (*B*) See text for discussion

variation of the parasystolic interval (between 118 and 172) appears quite unlikely in view of the stable rate of impulse formation observed in the preceding five electrocardiograms as well as in other leads of this particular tracing. Varying degrees of delay in exit from the parasystolic focus, as often invoked in explaining fluctuations of interectopic intervals, are also unlikely for the same reason. Hence one possible explanation is that beat 7 is an escape beat originating somewhere near the parasystolic focus, which did not disturb the parasystolic cycle as shown in the diagram.

In leads V and V (Fig 6 bottom) two and three parasystolic beats are seen, respectively with interectopic intervals of approximately 140. The first parasystolic beat in each lead (beat 3) represents ventricular fusion, as shown in the lower diagram. Although the timing of this fusion beat is similar to that of beat 3 in the top tracings, sinus P waves with identical contour continue to appear at relatively short intervals and the peculiar sequence of events as seen above do not occur in these leads.

PATIENT J M Parasystolic activity was demonstrated in six electrocardiograms. In a tracing reproduced in Fig 7 sinus rhythm showing left bundle branch system block is interrupted by frequent premature systoles with right bundle branch block configuration. In Lead V4, two single interectopic intervals containing one sinus beat each are seen measuring 132 and 156 respectively. Longer interectopic intervals seen in I, V1, and V are multiples of 142 to 144 as shown in the accompanying diagrams. Hence the calculated cycle lengths are shorter than the single cycles. Although similar observations were often made in other cases, the difference of 10 or greater between single and calculated cycle lengths was unusually great. Thus, this tracing showed the widest fluctuation of parasystolic intervals in the entire series of electrocardiograms studied, with a mean and standard error of 148.3 ± 1.96 (excluding those intervals discussed below). Daily variation of cycle lengths was also marked in this patient.

Furthermore, several interectopic intervals did not correspond to simple multiples of any of the cycle lengths (between 142 and 156) as shown above. For example, two parasystolic beats appear in Lead III with an interectopic interval of 256 (Fig. 7). If it is assumed that this represents two parasystolic intervals, the cycle length must be 128 and appears too short. Similarly V shows three parasystolic beats at intervals of 248 and 265. Again, an assumption of two parasystolic cycles in each interectopic interval will result in excessively short cycle lengths of 124 and 132.5 (see diagram *B*). In similar cases reported in the literature, intermittent parasystole has usually been invoked implying transient disappearance and later resumption of parasystolic activity. The following hypothesis is presented here as a possible mechanism of intermittence, as illustrated in the diagram below Lead III and diagram *A* below V.

If one measures the interval from the first sinus beat following a parasystolic beat to the next parasystolic QRS complex in these three instances, they turn out to be 148, 147 and 150, respectively and are almost identical to the mean parasystolic cycle length (148.3) calculated for this tracing. This relationship may suggest that the parasystolic pacemaker was discharged and its timing reset by this particular sinus impulse, implying temporary dissipation of protection around such focus. Return of the protective mechanism prevents successive discharge of the parasystolic pacemaker by the second sinus beat, thus resulting in the emergence of the next parasystolic impulse after its basic cycle length. However these arguments are entirely speculative, and the possibility of sudden acceleration (and deceleration) of the parasystolic focus cannot be excluded. If this latter explanation is adopted, the fluctuation of the parasystolic cycle length in this tracing becomes even more marked, with a mean and standard error of 140.5 ± 3.52. Hence, intermittent parasystole appears a more likely explanation. Three other electrocardiograms recorded on this patient similarly suggested the presence of intermittence.

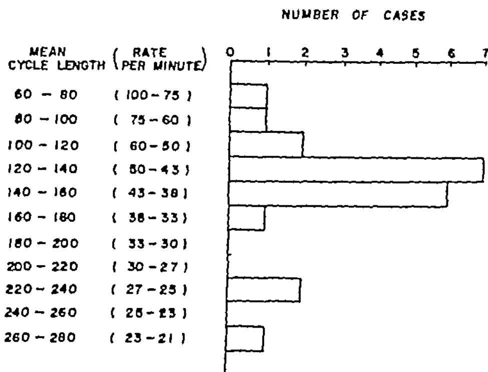


Fig 8 Distribution of mean parasystolic cycle lengths in 21 cases.

Studies on the entire group Table I summarizes all 21 cases with reference to the number of tracings recorded sinus cycle length the QRS configuration in the sinus beats mean parasystolic cycle lengths and the QRS configuration in the parasystolic beats. Distribution of the mean parasystolic cycle lengths in this group is shown in Fig 8 It is seen that 15 patients (71 4 per cent) had cycle lengths between 100 and 160 corresponding to rates between 60 and 38 beats per minute Two cases showed cycle lengths shorter than 100 or rates between 60 and 100 beats per minute while the remaining four instances had cycle lengths longer than 160 or rates slower than 38 beats per minute Hence the rate of parasystolic discharge in the majority of cases fell within the generally accepted range of intrinsic rhythmicity in the A V junctional or idioventricular pacemaker

A basic sinus rhythm was present in 19 of 21 patients while two patients showed atrial fibrillation No association was demonstrated between cycle lengths of the sinus pacemaker and that of the parasystolic focus. Nine patients showed marked sinus arrhythmias, as exemplified in patients B H J D and C. B discussed above The shortest parasystolic interval in the entire series (60 6) was observed in the presence of atrial fibrillation with a relatively rapid ventricular response (Patient J B) However the other patient with atrial fibrillation (F W) had a parasystolic length of 157 6 despite the presence of a similarly rapid ventricular response

Stability of impulse formation was studied by measuring all the parasystolic cycle lengths and calculating their mean and standard error in all 58 tracings. Nine electrocardiograms contained less than eight measurable parasystolic intervals, and hence were excluded from this statistical study Distribution of the standard errors in the remaining 49 tracings is shown in Table II It is noted that 22 tracings (45 per cent) had standard errors less than 0 5 indicating a remarkably stable rate of impulse formation Since the incidence of marked sinus arrhythmia was similar in groups showing smaller standard errors and larger standard errors (Table II) no direct relationship could be demonstrated between stability of sinus and parasystolic impulse formation On the other hand the number of instances where exit block from the parasystolic pacemaker was diagnosed with certainty was greater in the presence of smaller standard errors or more stable impulse formation than in the presence of more variable parasystolic intervals (Table II extreme right) This finding may

Table II *Stability of parasystolic rhythm*

Variation of parasystolic cycle length	Number of ECG	ECGs with marked sinus arrhythmia	ECG with exit block of parasystolic impulses
S.E. < 0.5	22	7	6
0.5 ≤ S.E. < 1.0	14	3	1
1.0 ≤ S.E. < 1.5	8	3	0
1.5 ≤ S.E. < 2.0	4	1	0
2.0 ≤ S.E.	1	1	0

S.E. = Standard error of mean.

simply reflect easier identification of exit block in instances having a constant parasystolic cycle length, although alternative possibilities will be presented in the discussion.

It was also noted that, when a parasystolic cycle length was calculated by dividing longer interectopic intervals, the cycle length tended to be somewhat shorter than that directly measured from the shortest or single interectopic intervals. This comparison was made in 41 electrocardiograms from 17 cases, and a mean and standard error of 146.4 ± 5.02 and 144.8 ± 4.98 were obtained for single and calculated cycle lengths, respectively. The difference between these two values (1.6 ± 0.61) was statistically significant ($P < 0.02$). On the other hand, single cycle lengths with one intervening sinus beat were longer than those containing no sinus beats. Thus, the cycle lengths containing one sinus beat and those without an intervening sinus beat obtained from six tracings in three patients were 122.5 ± 5.68 and 120.2 ± 6.45, respectively. The difference was again significant ($P < 0.02$). These findings may be related to different degrees of exit delay from the focus.

It is quite obvious that, if the site of impulse formation is located below the bifurcation of the His bundle, parasystolic beats should show grossly abnormal intraventricular conduction, while a parasystolic rhythm originating above the bifurcation would ordinarily show QRS similar to that of the sinus beats. As seen in Table I, certain degrees of intraventricular conduction disturbance were present with parasystolic beats in all 21 cases.

On the other hand, wide and bizarre QRS configuration of the sinus beats indicated an underlying intraventricular conduction delay in four patients. Two of these four patients showed left bundle branch block, while the other two showed right bundle branch block plus left anterior hemiblock. It should be noted that the two patients with left bundle branch block (C. B. and J. M.) were accompanied by parasystolic beats with right bundle branch block pattern. Fusion of sinus and parasystolic impulses resulted in more normal QRS contour (Fig. 5). Of the two cases where sinus beats showed right bundle branch block plus left anterior hemiblock, parasystolic beats showed right bundle branch block configuration in one (E. R.) and left bundle branch block with predominant delay in the anterior division in the other (D. H.). Ventricular fusion in these two cases also tended to produce narrower QRS complexes. In four additional cases, the sinus beats showed left anterior hemiblock with frontal QRS axis between −45 and −50 degrees. The pattern of parasystolic beats in these cases will be discussed later.

It is well known that, in the presence of ventricular parasystole, the end of ventricular refractory period can be localized within a narrow range, by determining the shortest coupling interval at which a parasystolic beat appears and the longest coupling interval at which propagation of an expected parasystolic impulse fails. On the other hand, the Q-T interval is generally considered to represent the duration of ventricular repolarization. It is true that more sophisticated electrophysiological

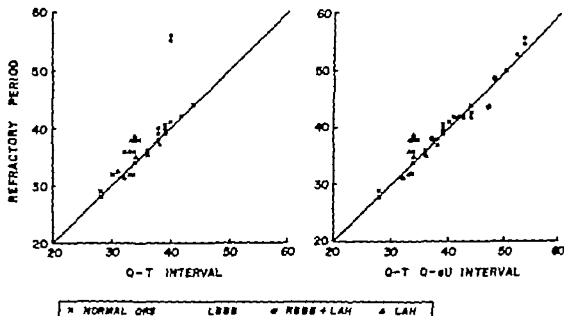


Fig 9 Correlation of refractory period as determined from the shortest coupling intervals of propagated parasystolic impulses and Q-T or Q-aU interval of the sinus beats. *LBBB* left bundle branch block *RBBB* right bundle branch block. *LAH* left anterior hemiblock in sinus beats.

studies utilizing microelectrodes have revealed that the relative duration of the effective refractory period and transmembrane action potential is not necessarily similar in different hearts or under different conditions[6,7] In clinical electrocardiography however the end of the effective refractory period and that of ventricular repolarization should still roughly coincide with each other

To test this relationship the duration of the ventricular refractory period was determined as precisely as possible in 55 tracings and plotted against the Q-T interval of the sinus beats in the same record The results are shown in Fig 9 left It is clearly seen that while many points fell along the expected 45-degree line the duration of refractory period is definitely longer than the corresponding Q-T interval in a considerable number of records. It is of particular interest that in 10 of the 14 tracings where the refractory period exceeded the Q T interval by more than 0 06 sec underlying bundle branch system block (8 with left bundle branch block and 2 with combined right bundle branch block and left anterior hemiblock) was present with sinus rhythm Furthermore most of these 14 tracings showed prominent U waves. Hence an attempt was made to correlate the refractory period with the Q-aU interval (interval from the onset of QRS to the apex of the U wave) in these instances. Replotting of these points resulted in a remarkable fit of the actual and theoretical values as illustrated in Fig 9 right.

Discussion

Mechanisms of parasystolic impulse formation Modern electrophysiological studies with recording of cardiac transmembrane potentials have established the role of slow diastolic depolarization as the basis of physiological impulse formation in the sinus node[8] So far this type of automaticity appears to be the only mechanism with which a single fiber or a group of fibers could generate regular impulses without requiring a preceding depolarization[3] This property is also shared by other specialized fibers of the atrioventricular conducting system including the intra-atrial conduction tracts A V junctional tissue and His-Purkinje system[9] Since parasystole is characterized by the maintenance of regular impulse formation in an ectopic site it is quite natural to invoke diastolic depolarization of certain specialized fibers

It has been pointed out by Scherf and others[10,11] that the frequency of impulse formation in ventricular parasystole often reaches 150 per minute a rate much higher for the physiological rhythmicity of the

His-Purkinje system Furthermore atrial parasystole usually exhibits a slower rate of impulse formation than physiological atrial or A V nodal pacemakers.[14] For these reasons, Scherf and others feel that parasystolic rhythms are abnormal and not caused by the automatic impulse originating in a protected center Instead these authors postulate a rapid impulse formation with various degrees of exit block in most or even all instances of parasystole[11] In contrast, the present series does not contain examples of parasystolic rhythm with rates higher than 100 per minute (Table I) This may possibly have resulted from failure of recognizing the patients with rapid parasystole However a higher rate itself does not contradict the concept of automaticity since an increased slope of diastolic depolarization in His-Purkinje fibers would readily cause more rapid impulse formation.

Mechanisms of protection of the parasystolic pacemaker intermittence and exit block At least two concepts can be found in the literature to explain protection of the parasystolic pacemaker from being discharged by the dominant cardiac impulses. Scherf suggests a high inherent frequency of discharge (often 300 per minute or higher) at the site of impulse formation which keeps the parasystolic pacemaker refractory to the invading excitation front.[11] Some degree of exit block or failure of propagation of impulses formed in the ectopic focus, must necessarily be postulated to explain much slower parasystolic activity observed in many cases including the present series The second theory invokes protection or entrance block around an ectopic pacemaker[17] Here the block must be unidirectional since it prevents the entrance of the sinus or other impulses into the pacemaking region while permitting the exit of impulses from this area. However the actual mechanism of protection has not yet been elucidated in any experimental study

Recently Singer and co-workers demonstrated that development of diastolic depolarization in His-Purkinje fibers with consequent reduction of membrane potential resulted in slow decremental conduction in this tissue Taking these observations into consideration Hoffman suggested that enhanced automaticity in a group of specialized fibers might create an ectopic pacemaker on one hand and provide the mechanism for entrance and exit block on the other[8] This hypothesis is quite unique in that one and the same electrophysiological phenomenon could explain both of the basic characteristics of parasystole or regular impulse formation within and protection around such focus.

If one subscribes to the above concept, rapid impulse formation of a pacemaker is not required as a protective mechanism and a parasystolic rhythm could result from a physiological degree of automaticity in the His-Purkinje system The present series showed a majority (71 4 per cent) of the 21 patients with a parasystolic rhythmicity compatible with normal A V junctional or His-Purkinje pacemaker and hence may support this view (Fig 8) Furthermore the persistence of a relatively constant parasystolic cycle length over seven years in one patient (B H Fig 1) and two years nine months in another (A. M O) both with a rate of approximately 50 per minute is definitely a finding against the concept of a rapidly firing focus associated with exit block. It seems extremely difficult to postulate a parasystolic pacemaker discharging at a high frequency of 300 per minute which remains active for over seven years and is accompanied by a constant 6 1 exit block.

However a parasystolic focus with rapid impulse formation is also recognized[23] In those examples of experimentally produced parasystole shown by Scherf and associates[11,24] high frequency of discharge undoubtedly played a role in protecting the site of impulse formation Thus the mechanism of protection may not be the same in all instances of parasystole.[3] Scherf also argues that protection may result from lowered excitability of the ectopic center relative to the strength of the sinus impulse[24] Some authors appear to be in favor of this concept. Similar argument may also explain the mechanism of exit block. However when one deals with the propagation of impulses between two groups of fibers having different excitability altered conductivity is almost inevitable and

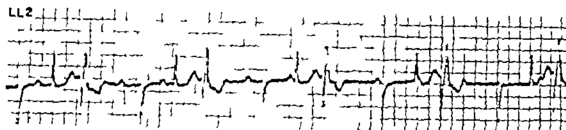


Fig. 10. The tracing shows a sinus rhythm at 86/min. but with a high grade A-V block. The QRS complexes not associated with stimulus artefacts of the electronic pacemaker are A-V junctional escape beats. Whenever a pacemaker stimulus coincides with the terminal portion of the T wave, successful ventricular depolarization occurs, while those stimulus artefact appearing in other parts of the cardiac cycle fail to produce QRS. Supernormal phase of ventricular excitability with lowered stimulus threshold appears to be the mechanism. In this instance A-V junctional escape rhythm is reset by such pacemaker induced beats, resulting in repetition of the same sequence of events.

hence the distinction between these two mechanisms may have little significance. The only definite example of exit block due to a lower excitability relative to the strength of stimuli is found in the presence of a malfunctioning electronic pacemaker (Fig. 10).

One argument against the concept of protection block around the parasystolic pacemaker has been that areas of unidirectional block are probably seen only under very special conditions[25] which might not persist for a prolonged period.[18] On the other hand, recent electrophysiologic al studies indicate that unidirectional conduction is not an uncommon finding in cardiac tissues with depressed conductivity.[32,34] Nevertheless, a certain number of fibers showing automaticity must necessarily be present to achieve both pacemaking and protective functions of parasystole. This is not an extremely difficult requirement since any factor causing diastolic depolarization in a group of His-Purkinje fibers may very well affect the adjacent area of the conducting system. Possible examples of escape beats showing similar QRS complexes as the parasystolic beats and at a slightly shorter cycle length than the parasystolic interval (Fig. 6) may actually have originated from such adjoining group of fibers.

It should further be pointed out that conduction between a parasystolic focus and the rest of the cardiac tissue does not always remain strictly unidirectional. Rather, block can become bidirectional as illustrated by the occasional appearance of exit block. One might argue that a greater degree of depression in conductivity around the parasystolic focus may on one hand provide a better protection but on the other hand increase the likelihood of exit block. As shown in Table II, the incidence of exit block appeared higher in the presence of more stable parasystolic cycle lengths. A stable interectopic interval may very well be the result of a better protection of the parasystolic pacemaker. The apparent association of exit block in these instances probably supports the above argument.

In contrast, if the depression of conductivity around the parasystolic pacemaker is less marked, propagation of the generated impulses (or exit) from the focus would be easier, resulting in lower incidence of exit block. At the same time, however, protection of the parasystolic pacemaker may be less effective and a sinus impulse may sometimes succeed in invading and discharging the focus. This would result in resetting of the parasystolic rhythm and hence intermittence. Wide fluctuation of the parasystolic cycle length seen in the case of possible intermittence (J. M., Fig. 7) most likely illustrates such an example. Scherf and Boyd argue that a sinus impulse arriving during the supernormal phase of excitability may reach the ectopic center and delay its impulse formation.[35] This may be considered a similar explanation for intermittence.

It has been pointed out that intermittent parasystole is usually initiated from a typical premature systole with fixed coupling interval.[17,33,34] One explanation proposed by Schamroth and Marriott[7] invokes either supernormal phase or the Wedensky effect. Apparently fixed coupling in the presence

of truly parasystolic, electronic pacemaker impulses can indeed be seen as in Fig 10 In this instance electronic impulses from the failing pacemaker are successfully propagated only during the terminal portion of the T waves, corresponding to the supernormal phase of ventricular excitability It is thus possible that in some cases of parasystole where the impulses formed in the focus are relatively weak periods of extrasystole with fixed coupling may be produced by impulses falling in the supernormal period or enhanced by the Wedensky effect Especially in those instances of parasystole showing transition into a bigeminal rhythm this explanation may be a plausible one. However an alternative explanation for the fixed coupling interval at the initiation of intermittent parasystole can be given as in Fig 7

If intermittence of a parasystolic activity indeed results from an incomplete or unstable protection and invasion of the focus by one or more sinus impulses, the parasystolic pacemaker must start its diastolic depolarization over again after every extrinsic discharge During such temporary dissipation of protective mechanism sinus impulses continue to discharge the focus and no parasystolic impulse can be formed However as soon as a more complete protection is restored diastolic depolarization in the parasystolic pacemaker is allowed to proceed and finally reach the threshold potential to form a parasystolic impulse This process requires a given amount of time, depending on the degree of automaticity The difference between this particular time interval and one (or two depending on the relative length of parasystolic and sinus cycles) sinus interval determines the coupling interval of the first parasystolic beat after a period of intermittence As long as both the parasystolic and sinus cycle lengths are reasonably constant, ther dif ference must also be constant. Hence the first coupling interval is fixed According to this concept, the first parasystolic beat following intermittence not coupled to the immediately preceding sinus beat but rather is coupled to the sinus beat appearing one cycle earlier One might even argu that more transient and occasional development of protective mechanism around a group of automatic fibers may cause an apparently coupled premature systole[17]

Furthermore since the so-called re-entry movement is also predicated upon an area of depressed conductivity with unidirectional block, it is possible that intermittent parasystole represents a link between the two fundamental mechanisms of arrhythmias, i.e. re-entry and automaticity [17]

Although not related to intermittent parasystole an apparently fixed coupling of parasystolic beats has often been identified [17] Discharge and resetting of the dominant (sinus) pacemaker by parasystolic impulses is one mechanism [24] and a simple mathematical relationship between the sinus and parasystolic cycle lengths is another to explain such phenomenon One patient (E R.) shown in Figs 3 and 4 may represent this latter mechanism Remarkably stable rates of impulse formation both in the sinus and parasystolic pacemakers must be present for the prolonged maintenance of fixed coupling interval. More commonly however such simple mathematical relationship of two rhythms appears only transiently and the coupling intervals tend to undergo a gradual change Maintenance of a constant interectopic interval with both progressive prolongation and shortening of the coupling intervals in the presence of marked sinus arrhythmia and bigeminal pattern would definitely establish the diagnosis of parasystole (Fig 2)

Sites of parasystolic impulse formation. If automaticity is a basic mechanism of parasystolic impulse formation a parasystolic pacemaker must consist of a group of specialized fibers in the A V conducting system rather than the working myocardial cells. In the instances of ventricular parasystole the focus is expected to be in some portion of the His-Purkinje system When diastolic depolarization develops in some Purkinje fibers, an association of depressed conductivity is most likely either secondary to diastolic depolarization or as a result of the same pathophysiologic factor causing automaticity Hence propagation of a sinus impulse through the area of a parasystolic focus must at least be delayed or rather blocked entirely as suggested in the preceding discussion on the protective mechanism.

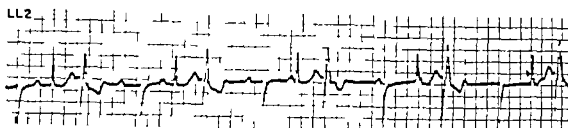


Fig 10 The tracing shows a sinus rhythm at 86/min but with a high grade A V block The QRS complexes not associated with stimulus artefacts of the electronic pacemaker are A V junctional escape beats. Whenever a pacemaker stimulus coincides with the terminal portion of the T wave successful ventricular depolarization occurs, while those stimulus artefacts appearing in other parts of the cardiac cycle fail to produce QRS. Supernormal phase of ventricular excitability with lowered stimulus threshold appears to be the mechanism. In this instance A V junctional escape rhythm is reset by such pacemaker induced beats, resulting in repetition of the same sequence of events.

hence the distinction between these two mechanisms may have little significance The only definite example of exit block due to a lower excitability relative to the strength of stimuli is found in the presence of a malfunctioning electronic pacemaker (Fig 10)

One argument against the concept of protection block around the parasystolic pacemaker has been that areas of unidirectional block are probably seen only under very special conditions[22] which might not persist for a prolonged period [19] On the other hand recent electrophysiological studies indicate that unidirectional conduction is not an uncommon finding in cardiac tissues with depressed conductivity [23,24] Nevertheless a certain number of fibers showing automaticity must necessarily be present to achieve both pacemaking and protective functions of parasystole This is not an extremely difficult requirement since any factor causing diastolic depolarization in a group of His-Purkinje fibers may very well affect the adjacent area of the conducting system Possible examples of escape beats showing similar QRS complexes as the parasystolic beats and at a slightly shorter cycle length than the parasystolic interval (Fig 6) may actually have originated from such adjoining group of fibers.

It should further be pointed out that conduction between a parasystolic focus and the rest of the cardiac tissue does not always remain strictly unidirectional Rather block can become bidirectional as illustrated by the occasional appearance of exit block One might argue that a greater degree of depression in conductivity around the parasystolic focus may on one hand provide a better protection but on the other hand increase the likelihood of exit block As shown in Table II the incidence of exit block appeared higher in the presence of more stable parasystolic cycle lengths A stable interectopic interval may very well be the result of a better protection of the parasystolic pacemaker The apparent association of exit block in these instances probably supports the above argument

In contrast if the depression of conductivity around the parasystolic pacemaker is less marked propagation of the generated impulses (or exit) from the focus would be easier resulting in lower incidence of exit block At the same time however protection of the parasystolic pacemaker may be less effective and a sinus impulse may sometimes succeed in invading and discharging the focus. This would result in resetting of the parasystolic rhythm and hence intermittence Wide fluctuation of the parasystolic cycle length seen in the case of possible intermittence (J M Fig 7) most likely illustrates such an example Scherf and Boyd argue that a sinus impulse arriving during the supernormal phase of excitability may reach the ectopic center and delay its impulse formation [22] This may be considered a similar explanation for intermittence

It has been pointed out that intermittent parasystole is usually initiated from a typical premature systole with fixed coupling interval [17,22,25] One explanation proposed by Schamroth and Marriott[4] invokes either supernormal phase or the Wedensky effect Apparently fixed coupling in the presence

it is now well known that the duration of the action potential as well as refractory period is longer in Purkinje fibers than in ventricular muscle fibers,[1] the earliest parasystolic beat in those instances must show a longer coupling interval than the Q-T interval. The present observation of refractory periods longer than the Q-T interval in patients with underlying bundle branch system block appears to support this hypothesis (Fig 9 left)

3 It was further noted that those instances with longer refractory periods were associated with prominent U waves, and the end of the refractory period coincided with the apex of the U wave (Fig 9 right) This finding strongly suggests that the U wave of the electrocardiogram might represent the terminal phase (phase 3) of repolarization in the His-Purkinje system In one case of left bundle branch block (Patient J M) the end of the refractory period roughly corresponded to the U wave in four of the six tracings where prominent U waves were present. In the remaining two electrocardiograms from this same patient, U waves were indiscernible in the entire twelve leads, and the earliest parasystolic beats appeared at the end of the Q-T interval This probably indicates relative shortening of the Purkinje action potential with almost simultaneous repolarization of Purkinje and ventricular fibers, since a shift of the parasystolic focus could be ruled out both from the cycle length and QRS configuration.

Based on these concepts, location of the parasystolic pacemaker within the major fascicles of the intraventricular conducting system was suggested in six patients (R. A. C. B N D D H J M and E. R.) The rate of impulse formation in these six patients ranged from 39 to 59 beats per minute (Table I Fig 8) Possible A V junctional origin was suggested in two (M J and H K.) while the remaining 13 cases most likely had more peripheral Purkinje focus.

Summary

Fifty-eight electrocardiograms from 21 patients showing parasystole were studied both individually and as a group. Several interesting cases were presented to illustrate (1) parasystolic activity of long duration (one over 7 years and the other 2 years and 9 months) (2) parasystole causing periods of ventricular bigeminy with both progressive prolongation and shortening of the coupling interval (3) possible example of a parasystolic rhythm with fixed coupling interval (4) complex arrhythmia caused by parasystole and escape beats originating from the region of parasystolic focus and (5) an example of intermittent parasystole Furthermore (6) distribution of the mean parasystolic cycle lengths (7) stability of parasystolic impulse formation and its relationship with exit block (8) the relationship between the QRS configuration of the sinus and the parasystolic beats and (9) the correlation between the refractory period and the Q-T or Q-aU interval of the sinus beats were studied in the entire group.

These studies suggest automaticity in some portions of the specialized conducting system as the most likely mechanism of both parasystolic impulse formation and protection of such parasystolic focus. The relationships between the protective mechanism and exit block as well as intermittence were also discussed Finally the following hypotheses were presented (1) Parasystolic focus is most likely located in one of the major bundle branches or fascicles when sinus beats show intraventricular conduction disturbances, while the focus is located more peripherally in the Purkinje system when sinus beats show normal QRS duration, and (2) the U wave of the electrocardiogram may very well represent the repolarization process in the Purkinje system

REFERENCES

1 Hoffman, B. F and Cranefield, P F The physiological basis of cardiac arrhythmias, Amer J Med. 37:670, 1964.
2. Watanabe, Y and Dreifus, L. S. Newer concepts in the genesis of cardiac arrhythmias, Amer. Heart J 76 114 1968.
3 Schamroth, L., and Marriott, H. J L. Intermittent ventricular parasystole with observations on its relationship to extrasystolic bigeminy Amer J Cardiol. 7 799 1961.
4. Goldenberg, M and Scherf, D. Zur Entstehungsweise der fest gekuppelter Extrasystolen, Wien. Arch. Inn. Med. 15:357 1928.
5 Pick, A. Parasystole, Circulation 8:243 1953.
6. Bigger J T J Bassett, A. L., and Hoffman, B F., Electrophysiological effects of diphenyl-

It then follows that in those instances where sinus beats show narrow QRS complexes the parasystolic pacemaker most likely is located in a relatively peripheral ramification of the Purkinje fibers so that over all ventricular activation by sinus impulse is not significantly altered Contrarily if a parasystolic focus is located within one of the major fascicles of the intraventricular conducting system the pattern of ventricular excitation in sinus beats may be grossly altered In other words in those cases with underlying bundle branch block the parasystolic pacemaker is probably located in the bundle branch showing conduction delay This assumption appears supported by the fact that in the two cases of parasystole where sinus beats showed left bundle branch system block (Patients C B and J M) the parasystolic beats showed a right bundle branch block configuration suggesting impulse formation in the left bundle branch system (Table I Fig 5) Of the two patients with combined right bundle branch block and left anterior hemiblock one (D H) showed parasystolic beats with left bundle branch block (particularly left anterior hemiblock) configuration The parasystolic focus in this case was probably located in the right bundle branch The other patient (E R) showed parasystolic QRS compatible with right bundle branch block alone suggesting the origin of these beats in the anterior division of the left bundle branch When an ectopic impulse is originated in one of the three major fascicles of intraventricular conducting system ventricular activation may show apparent conduction delay in the remaining two fascicles. However pre-existing block in one of these two fascicles should result in a QRS configuration showing predominant delay in this blocked fascicle

Similarly two of the four patients with underlying left anterior hemiblock (R A and N D) were associated with parasystolic beats showing possible left posterior hemiblock pattern (QRS axis +105 and +130 degrees, respectively) In the absence of right bundle branch block such QRS configurations may be expected when an impulse originates in the anterior division of the left bundle On the other hand the other two patients with left anterior hemiblock (M J and H K) showed maintenance of the same hemiblock pattern in parasystolic beats although the QRS axis and configuration were slightly changed Here an A V junctional origin of parasystole cannot be ruled out.

It has been pointed out by Pick[3] that in some instances of parasystole the duration of ventricular unresponsiveness as determined by the range of coupling intervals is considerably longer than the Q-T interval of the sinus beats. To explain this finding he stated that the electrical phenomenon of repolarization does not necessarily coincide temporally with a functional phenomenon related to the hearts excitability Similar discrepancy between the refractory period and the Q-T interval was noted in the present study especially in the presence of underlying bundle branch block (Fig 9 left) Since these cases showed prominent U waves their refractory period was replotted against the Q-aU interval instead of Q T interval This resulted in a remarkable fit of these two variables as shown in Fig 9 right.

These observations are of extreme interest with regard to the following considerations

1 Since the end of the T wave should roughly coincide with the end of the ventricular refractoriness in clinical electrocardiograms the coupling interval of the earliest parasystolic beats must be almost identical to the Q-T interval if propagation of parasystolic impulses is controlled by the refractory period of the ventricular muscle This was actually the case in a majority of tracings particularly where the sinus beats showed normal intraventricular conduction This finding may indicate proximity of a parasystolic focus with the ventricular myocardium and may very well support the above mentioned concept of a peripheral localization of the parasystolic pacemaker in those instances

2 It can be theorized that when a parasystolic focus is located within the more proximal bundle branches, such pacemaker is surrounded by Purkinje fibers and hence the exit of parasystolic impulses is probably controlled by the duration of refractory period in these Purkinje fibers Since

A comparison of T wave inversion, S-T elevation, and RS amplitudes in precordial leads of Africans and Indians in Guyana

M. T. Ashcroft, D.M., M.R.C.P., D.P.H., D.T.M.&H.
G. J. Miller, M.B., Ch.B., M.R.C.P.
H. M. S. G. Beadnell, M.R.C.S., L.R.C.P.
A. V. Swan, M.Sc.
Kingston, Jamaica, and Lusignan, Guyana

There have been many studies of the possible differences between ECG's of African and Caucasian groups since Littman in 1946 noted that T wave inversion in precordial leads was more common among apparently healthy Negro than among Caucasian Americans. Other ECG items which may be influenced by racial origin include S-T elevation and the amplitude of R and S waves in precordial leads. The considerable work on this subject has recently been comprehensively reviewed.[1]

In the South American republic of Guyana (formerly known as British Guiana) people of African and Indian origin live side by side in similar socioeconomic circumstances. An excellent opportunity, therefore, exists for comparing electrocardiograms (ECG's) from two distinct ethnic groups using the same recording and coding techniques, thereby avoiding the many uncertainties which arise when comparing results obtained in different surveys.

Age, obesity, blood pressure, and cardiothoracic ratios are recognized as influencing ECG patterns, particularly QRS amplitudes, and the importance of those factors in explaining the observed ethnic differences is assessed.

Population and methods

A private census was taken of two adjacent communities, Annandale and Buxton, situated on the coast about twelve miles east of Georgetown, the capital. The inhabitants of Annandale are mostly Indians (referred to in Guyana as East Indians to distinguish them from Amerindians) whose forebearers came in the years between 1846 and 1917 from India as indentured laborers. People from Buxton are for the most part descendents of persons brought from Western Africa in the eighteenth and early nineteenth centuries.

Indians have remained racially distinct and Africans have mixed to a small extent only with Europeans. Many Indian men worked on sugar plantations, whereas the occupations of African men were more varied. The majority of men of both ethnic groups were engaged in employment requiring a high level of physical activity.

From the Medical Research Council Epidemiology Unit, University of the West Indies, Kingston, Jamaica, and Guyana Sugar Producers Association Hospital, Lusignan, Guyana.
Received for publication May 18, 1970.
Reprint requests to: Dr. M. T. Ashcroft, MRC Epidemiology Unit, University of the West Indies, Kingston, Jamaica.

hydintion on canine Iurkinje fibers Circ Res 22:221 1968
7 I ommtuan J Dreifu I S and Watanabe Y Comparitive mechani m of antiarrhythmic agent Amer J Cardiol 26:51 1970
8 Hoffman B F and Cranefield P F: Electrophysiology of the heart New York 1960 Mc Graw Hill Book Company Inc
9 Hoffman B F The electrophysiology of the heart muscle and the genesis of arrhythmias, in Dreifu I S and Likoff W editors Mechanism and therapy of cardiac arrhythmias, New York 1966, Grune & Stratton Inc p. 27
10 Scherf D and Bornemann, C Pare y tole with a pid ventricular center Amer Heart J 62:320 1961
11 Scherf D Choi K B, ha lom A and Orpha nos, R J Para y tole Amer J Cardiol 11:5 7 1963
12 Scherf D Bornemann C and Yild M A V nodal para y tole Amer Heart J 60:179 1960.
13 Chung K Walsh T J and M se I Atrial para y tole Amer J Cardiol 11:255 1961
14 Eliakim M Atrial para y tole Amer J Cardiol 16:457 1965
15 Scherf D Zur Entst h n g weise der Extra systolen und der extra s t lischen Allorhyth mien Z Ges Exp Med 51:816 19 6.
16 Kaufmann R and Rothberger C J Beitrag zur K ntni der E t teh ing weise der xt a ystolischen Allorhythmien Z Ges Exp Med 5:319 1917
17 Kat L N and Pick A Cl l electr cardiog phy Part I The rrhyth s, Phil delphia 1956 Lea & Febiger Publisher
18 Singer D H Lazzara R and Hoffman B F Interrelationship between u ti m tivity and conduction in Purkinje fibers, Circ. Res. 1:537 1967
19 Scherf D Experimental para ystole Amer. Heart J 4 :212 1951
0 Scherf D Chick F B, Scharf M M and Terr inova R. Further studies on experimental para ystole and extra y toles in groups, Proc. Soc. Exp Biol. Med 77:28 1951
21 Scherf D and Schott A Extrasystoles and allied rrhythmias, London, 1953 William H nemann
2 Schmitt F O. and Erlanger J Directional differences in the conduction of impulse through heart muscle and their possible relation to extrasystolic and fibrillary contractions, Amer J Physiol 8 :326, 1928.
23 Watanabe, Y and Dreifus, L S. Inhomogeneous conduction in the A V node. A model for re-entry Amer Heart J 70:505 1965
24 Han J Millozzi, A M and Moe G K. Sinoatrial reciprocation in the isolated rabb t heart Circ Res. 22:355 1968.
25 Scherf D and Boyd L. J Three unusual cases of parasystole Amer Heart J 39:650 1950
26. Mueller P nd Baron, B Clinical studies on par y t le Amer Heart J 1 :141 1953.
7 Langendorf R and Pick, A Mechanisms of intermittent ventricular bigeminy II Para sy tole and para yst le or re-entry with conduct n di turbance Circulation 11:431 1955.
28. Scherf D Schott A Reid E C nd Chamsai, D G Intermittent para ystole Cardiologia 30:217 1937
29 Hoffman B F Physiologic basis of d turbances of card c rhyth n a d conduction Progr Cardiovasc D s :319 1959
30 Scherf D and Yildiz M Atrial parasy tole Amer Heart J 57:507 1959

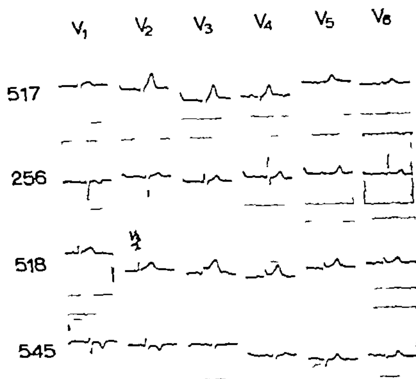


Fig. 1 Typical precordial leads Guyanese adults. No. 517 Man aged 40. Typical male pattern with upright T wave in V No. 256 Woman aged 42. Typical female pattern with inverted T wave in V but upright in leads to left. No. 518 Man aged 51 S-T segment elevation in V and V No. 545 Woman aged 50. Inverted T waves in V V and V suggesting juvenile pattern.

Table I Percentage prevalence of T wave changes in precordial Leads V V and V of African and Indian men and women

Sex	Group	N of ECG'	V			V			V		
			Inverted	*Diphasic*	*Flat*	*Inverted*	*Diphasic*	*Flat*	*Inverted*	*Diphasic*	*Flat*
Men	African	160	9 4	10 0	1 9	0 6	1 3	—	—	1 9	—
	Indian	213	9 8	8 5	4 7	—	1 4	—	—	0 9	—
	Total	373	9 6	9 2	3 5	0 3	1 3	—	—	1 3	—
Women	African	239	45 6	5 9	8 4	2 9	2 1	2 3	2 1	1 3	—
	India	218	47 2	5 0	9 6	4 1	0 5	2 3	2 8	0 5	0 9
	Total	457	46 4	5 5	9 0	3 5	1 5	2 4	2 4	0 9	0 4

the 19 African and 18 Indian women with nonupright T waves (Table II) No significant differences in these factors were found between those with upright and those with nonupright T waves.

S-T elevation S-T elevation was significantly more common in African men (18 1 per cent) than in Indian men (13 6 per cent) and was unusual in African women (2 1 per cent) and Indian women (0 9 per cent) (Table III) S-T elevation was seen most frequently in Lead V_4.

Almost all the women described themselves as housewives but some worked in cane fields or sold products in local markets. Standards of living were reasonably good.

All persons on the census who were aged 35 to 54 years were given appointments to attend Lusignan Hospital. Most subjects knew their ages accurately and were able to show birth certificates. Attendance from the two communities was arranged for alternate days so that any variations in technique would be evenly distributed for the two races. A total of 860 subjects were seen. The response rate was 72.5 per cent for African men, 83.1 per cent for African women, 78.5 per cent for Indian men, and 83.1 per cent for Indian women.

Following a personal and medical history, anthropometric measurements including height, weight, and subscapular skinfold thickness were made. The cardiovascular system was examined clinically and blood pressure was estimated in the left arm with a standard sphygmomanometer. A 12 lead ECG was taken using a Cambridge direct-writing machine, employing the same technician and the same instrument throughout the survey. A posterior-anterior radiograph of the chest in full inspiration was taken with a standard apparatus with the tube distance at 6 ft. The cardiothoracic ratio (CTR) was estimated from the transverse diameter of the heart and the maximum internal thoracic diameter between the ribs. Venous blood was taken for estimation of hemoglobin and serum cholesterol. Details of the anthropometric results and of the cardiovascular survey have been reported separately.[3,4]

ECG's were all examined by one observer (M. T. A.). Thirteen subjects with valvular disease, atrial fibrillation, or bundle branch block were excluded from the analysis, as were 17 subjects who were pregnant or who were not of predominantly African or Indian origin. Hypertensive subjects, unless suffering from the above conditions, were not excluded. ECG's of 160 and 239 African men and women and 213 and 218 Indian men and women, respectively, remained for analysis.

T waves were coded as inverted if their lowest amplitudes were at least 0.5 mm below the isoelectric line (T-P) segment. A depression or elevation of less than 0.5 mm was coded as a flat T wave. T waves with negative and positive phases of more than 0.5 mm were coded as diphasic. A typical inverted T wave in V_1 is shown in ECG No. 256 in Fig. 1. T wave changes in the right precordial leads (V_1 to V_3) but not in V_4 to V_6 were analyzed.

S-T segments were coded as elevated if the J junction was followed by a concave S-T segment with its initial direction pointing horizontally or downward and with its lowest point at least 1.0 mm above the isoelectric line, as in Leads V_3 and V_4 in ECG No. 518 in Fig. 1. These criteria were adopted to avoid the difficulty of ascertaining the true position of J when the ascending limb of an S wave merges without obvious change into the S-T segment as in Lead V_2 of ECG No. 517. All precordial leads were inspected for S-T elevation.

S wave amplitudes were measured in V_1 and R wave amplitudes in V_5 and V_6.

Results

T wave changes. Percentage prevalences of inverted, flat, and diphasic T waves in Leads V_1, V_2, and V_3 are shown in Table I. No ethnic differences were found but sex differences were marked. In V_1 inverted and flat T waves were found in 46.4 per cent and 9.0 per cent, respectively, of women (combining the two races) compared to 9.6 per cent and 3.5 per cent of men. In contrast, diphasicity in V_1 was less common in women (5.5 per cent) than in men (9.2 per cent). The usual male pattern in V_1 was an S-T segment bowed upward, occasionally followed by a terminal dip of the T wave giving rise to diphasicity. The usual female pattern was a flat S-T segment followed by an inverted T wave. Nonupright (inverted, diphasic, or flat) T waves in Leads V_2 and V_3 were found in 7.2 per cent and 3.7 per cent, respectively, of women and in 1.6 per cent and 1.3 per cent of men. Inverted T waves in V_2 and V_3 occurred in 3.5 per cent and 2.4 per cent, respectively, of women but in none of the men.

Mean subscapular skinfold thickness, systolic and diastolic blood pressure levels, and serum cholesterol were calculated for

Table IV Characteristics of African and Indian men with and without S-T elevation in precordial leads

Variable	African men				Indian men			
	With S-T elevation n = 29		Without S-T elevation n = 131		With S-T elevation n = 29		Without S-T elevation n = 183	
	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
S-V amplitude (mm.)	13 8	5 6	11 7	5 6	11 1	5 0	9 5	4 9
R-V amplitude (mm.)	23 0	6 6	19 6	6 8	20	7 4	16 8	7 6
R V amplitude (mm.)	15 3	4 3†	13 4	4 2	13 0	4 9*	11 2	4 6
Diastolic pressure (mm Hg)	85 0	14 4	86 3	15 1	78 4	9 1	81 5	14 6
Pulse rate per min.	74 1	8 8	77 3	12 6	63 1	11 1	77 9	10 7†

*p 0 05 > 0 01 for differences between subjects with and without S-T elevation.
†p 0 01 for differences between subjects with and without S-T elevation.

Table V Amplitudes (mm.) of S wave in V₁ and R waves in V and V₆ at various blood pressure levels comparing Africans Indians and Caucasians

Sex	Variables	Ethnic group	No. of ECG	S in V amplitude (mm.)		R in V amplitude (mm.)		R in V amplitude (mm.)	
				Mean	S D	Mean	S.D	Mean	S D
Men	All subjects	African	160	12 2	5 3†	20 2	6 8†	12 9	4 3†
		Indian	213	9 7	4 9	17 5	7 7	11 4	4 7
	Blood pressure <160/95 mm. Hg	African	111	11 6	5 3†	18 9	5 7†	12 0	3 8
		Indian	144	9 5	4 5	16 4	3 7	10 9	3 9
		Caucasian[a]	424	8 6	3 6	14 1	4 8	10 5	3 5
	Systolic pressure <120 mm Hg	African	41	10 8	5 5	19 5	5 7†	12 0	3 6
		Indian	75	9 1	4 6	13 8	3 7	10 2	3 3
Women	All subjects	African	239	9 9	4 3†	14 6	4 9†	10 6	3 6
		Indian	218	8 9	3 9	12 4	5 3	9 3	3 4
	Blood pressure <160/95 mm. Hg	African	138	9 1	4 2	13 9	4 3†	9 9	3 1†
		Indian	137	8 3	3 2	11 4	4 5	8 6	2 9
		Caucasian[a]	142	7 2	3 2	11 6	3 9	9 6	3 2
	Systolic pressure <120 mm Hg	African	53	9 1	3 9*	14 0	4 6†	10 2	3 6
		Indian	83	7 9	3 3	10 9	3 5	8 2	2 6

*p 05 0 01 for amplitude differences between Africans and Indians.
†p < 0 01 for amplitude differences between Africans and Indians.

ments are presented in Table VI and regression coefficients (expressed in standard deviation units) in Table VII In general age and subscapular skinfold coefficients were negative but only the latter were large enough to be of importance. Systolic pressure coefficients were positive and frequently statistically significant although diastolic pressure coefficients, rather surprisingly showed no definite pattern. CTR coefficients for R, but not for S waves, were also positive and often significant These results confirm previous recognition that obesity probably

Table II Characteristics of African and Indian women with and without nonupright T waves in Leads V_5 or V_6

Variables	African women				Indian women			
	With nonupright T waves n = 19		With upright T waves n = 220		With nonupright T waves n = 18		With upright T waves n = 200	
	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
Subscapular skinfold (mm)	31 4	11	31 5	11 1	7 1	14	31 9	13 4
Systolic pressure (mm Hg)	133 8	5 1	141	7 2	121 1	30 0	132 0	28 5
Diastolic pressure (mm Hg)	85 5	13 3	88 4	15 6	79 4	16 1	84 7	15 3
Serum cholesterol (mg per 100 ml)	218 0	37 8	08 4	33 2	206 5	26 5	105 3	39 7

Differences between subjects with and without upright T waves are not significantly different from zero at the 5 per cent level

Table III Percentage prevalence of S-T elevation in precordial leads of African and Indian men and women

Sex	Groups	No of ECG's	V_1	V_2	V_3	V_4	V_5	V_6	ECG's with S-T elevation
Men	African	160	—	1 9	6 9	11 3	8 8	1 9	18 1
	Indian	213	0 5	0 9	5 2	9 4	3 8	2 3	13 6
Women	African	239	—	0 4	1 3	0 4	—	—	2 1
	Indian	18		—	0 9	—	—	—	0 9

Mean amplitudes of the S wave in V_1 and R waves in V_5 and V_6, mean diastolic pressure and pulse rate were estimated for the 29 African and 29 Indian men with S-T elevation and compared with mean values of subjects with no S-T elevation (Table IV)

S-T elevation was associated with significantly larger R amplitudes in V_5 and V_6 and larger S waves in V_1. Mean pulse rate and diastolic pressure were lower (significantly so in Indians) in those with S-T elevation

Amplitudes of S waves in V_1 and R waves in V_5 and V_6. In Table V means and standard deviations of S-wave amplitude in V_1 and R wave amplitudes in V_5 and V_6 are shown for all subjects for those with blood pressures below 160 mm Hg systolic and 95 mm Hg diastolic and for those with systolic pressures below 120 mm Hg. Also shown are S and R amplitudes previously reported for Caucasian adults aged 40 to 59 years with blood pressure levels below 160 95 mm. Higher mean amplitudes were found in Africans than in Indians of both sexes at all levels of blood pressure. Amplitudes quoted for Caucasian men were in general lower than those of Indian men but no consistent differences between Caucasian and Indian women were apparent

Multiple regression analyses were performed within the 4 sex race groups (African men and women Indian men and women) regressing the amplitudes of S in V_1 and R in V_5 and V_6 on age, subscapular skinfold thickness, systolic pressure, diastolic pressure and CTR. Means and standard deviations of these measure-

but also had higher mean blood pressures and greater CTR's than Indian women (Table VI). These ethnic differences (except for fatness in women) would operate so as to explain at least partially the higher amplitudes of S and R waves in Africans.

Further statistical analysis was undertaken to predict the extent to which these factors were responsible for observed amplitude differences. Regression coefficients for the variables did not differ significantly between Africans and Indians and therefore regression coefficients applicable to both races were calculated for each sex. Using these coefficients, the predicted differences between the two races in wave amplitudes were estimated from the racial differences in mean values for age, subscapular skinfold, systolic pressure, diastolic pressure, and CTR. Predicted differences were considerable and most of them were significantly smaller than observed differences (Table VII). The ethnic difference in wave amplitude is, therefore, only partially explained by differences in age, obesity, blood pressure, and cardiothoracic ratio.

Comparison with T-wave patterns reported by other workers is difficult, not only because differences in technique may be important, but also because the patterns under consideration have sometimes been loosely defined and the possibility arises that dissimilar items are being compared. Some investigators have not distinguished between diphasic and inverted T waves and the degree of negativity required before a T wave is coded as negative rather than flat has not always been stated. The patterns themselves are not stable and are liable to change in a variety of circumstances. An important omission in reporting results is that findings in men and women have not always been reported separately. A few of the more relevant studies will be considered.

Gottschalk and Craige compared T waves in 600 healthy young Negro and Caucasian adults of both sexes in the United States. Their findings in Negroes were similar to those in Guyana. In Leads V_1 to V_3 inverted and flat T waves were more common in women than in men but diphasic waves were found more often in men. Inverted T waves in V_2 and V_3 occurred in none of the men and in a small proportion of the women. Nonupright T waves in all three leads were more common in Negro than in Caucasian subjects. Walker and Walker[3] reported T wave inversion in several groups of Bantus and Caucasians in South Africa. T wave inversion in V_1 was more common in women than in men. Among the Bantus, T wave inversion in V and V occurred in 4.1 per cent and 0.7 per cent of men, respectively, and in 5.0 per cent and 0.6 per cent of women. T wave inversion was found in 3.1 per cent of Caucasian women in V_2 but was not seen in V_3; no Caucasian men had T wave inversion in either V_2 or V_3. Brink[7] found T wave inversion in V_2 and V_3 in 12 per cent and 6 per cent, respectively, of male Bantus; in the females 8 per cent of T waves were inverted in V, but no inversion occurred in V_3.

In Bantu patients (sex not specified) and healthy female nurses in a South African hospital, Grusin[8] noted a common ECG pattern in right precordial leads in which the S-T segment was bowed upward and followed by a negative phase of the T wave. The pattern was described as S-T depression and T wave inversion but the S-T depression was dependent on the J junction on the rising limb of an S wave being below the isoelectric line. The location of J is, however, difficult and the pattern appeared to resemble in an exaggerated form that defined in this paper as T wave diphasicity, a pattern which was not uncommon in Lead V_1 in men. A notable feature was the variability of Grusin's T-wave patterns in ECG's repeated on the same subject.

The three investigations are cited as examples of the divergencies in T wave patterns, some of which may be due to techniques or definition and some of which may be real, which have been recorded among subjects of related ethnic groups. As has been rightly pointed out,[3] generalizations about ethnic differences in T wave patterns must be made with care.

Accurate comparison previously reported in prevalences of S-T elevation is also difficult because S-T elevation has sometimes been defined (if defined at all) as

Table VI Means and standard deviations of age subscapular skinfolds systolic and diastolic pressures and cardiothoracic ratios of African and Indian men and women

Sex	Groups	No	Age (yr.)		Subscapular skinfold (mm.)		Systolic pressure (mm. Hg)		Diastolic pressure (mm. Hg)		Cardiothoracic ratio (%)	
Men	African	160	45.0	5.7	13.6	8.8†	136.9	24.4	86.0	14.9	47.6	4.3
	Indian	213	44.4	6.3	17.1	10.9	131.4	23.6	83.7	14.1	46.7	4.4
Women	African	239	44.9	5.5	31.8	15.8	140.6	27.1†	88.2	15.4	50.9	4.6
	Indian	218	44.0	6.2	31.5	13.5	131.1	28.7	81.3	16.3	50.2	5.1

*$p < 0.05 > 0.01$ for differences between Africans and Indians.
†$p < 0.01$ for differences between Africans and Indians.

Table VII Multiple regression analysis of amplitudes of S wave in V_1 and R waves in V_5 and V_6 on age subscapular skinfold systolic and diastolic pressures and cardiothoracic ratio

Dependent variable	Sex	Ethnic origin	Per cent of variation accounted for	Regression coefficients of independent variables in S.D. units					Observed amplitude difference (mm.)	Predicted amplitude difference (mm.)
				Age	Subscapular skinfold	Systolic BP	Diastolic BP	Cardiothoracic ratio		
Amplitude of S in V	Men	African	10.7	−0.20*	0.00	0.42*	−0.19	0.13	2.6	0.35†
		Indian	4.6	−0.05	−0.11	0.16	0.06	0.06		
	Women	African	13.2	−0.01	−0.14	0.41	−0.03	0.04	1.0	0.50
		Indian	12.2	−0.02	−0.09	0.45	−0.13	−0.06		
Amplitude of R in V	Men	African	11.6	−0.05	−0.11	0.15	0.00	0.25	2.7	0.61†
		Indian	22.1	−0.11	−0.[illegible]	0.31	0.01	0.23		
	Women	African	11.5	0.02	−0.22*	0.13	0.17	0.15	2.2	0.41†
		Indian	13.1	0.01	−0.15*	0.21	0.02	0.19*		
Amplitude of R in V	Men	African	12.5	−0.07	−0.02	0.[illegible]0*	−0.09	0.26*	1.6	0.60
		Indian	17.3	−0.10	−0.1	0.36*	−0.07	0.23*		
	Women	African	11.6	−0.04	−0.10*	0.12	0.13	0.09*	1.3	0.25†
		Indian	12.4	−0.03	−0.14	0.[illegible]3	0.06	0.16*		

*Significantly different from zero ($p < 0.05$)
†Predicted difference significantly different from observed difference ($p < 0.05$)

by its effect on electrical conduction reduces whereas hypertension and large CTR's increase the amplitudes of the R and S waves under consideration

Discussion

This study revealed significant differences between some ECG patterns of African and Indian adults S-T elevation was more prevalent and the amplitude of the S wave in V_1 and R waves in V_5 and V_6 were significantly higher in Africans than Indians. The prevalence of nonupright T waves in V_1 V_2 and V_3 was, however, similar in the two ethnic groups. It was noteworthy that sex dissimilarities in ECG patterns were more prominent than ethnic dissimilarities. Nonupright T waves in V_1 to V_3 were less common and S-T elevation and high amplitude S and R waves were much more common in men than in women

The results were not due to differences in techniques which were the same for all subjects in the survey R and S-wave differences might however be explained by ethnic variation in one or more factors which influence wave amplitude. African men were thinner had higher mean blood pressures and greater CTR's than Indian men African women were slightly fatter

results recorded from Guyana demonstrate that allowance should be made for sex and ethnic differences.

Summary

ECG precordial leads of 830 Guyanese men and women of African and Indian origin aged 35 to 54 years were compared The prevalence of nonupright T waves in right precordial leads (V to V) were simi lar in the two ethnic groups. T wave inver sion in V_1 V_2, and V was present in 46 4 per cent, 3.3 per cent and 2 4 per cent of women respectively compared with 9 6 per cent in V_1 and no inversion in V and V in men S-T elevation occurring in any of the precordial leads was present in 2 1 per cent of African women 0 9 per cent of Indian women 18 1 per cent of African men and 13 6 per cent of Indian men

Neither T-wave inversion in right pre cordial leads nor S-T elevation were as- sociated with detectable clinical abnor mality hypertension obesity or raised blood cholesterol levels and both appeared to be normal variants. S-T elevation was associated with large QRS complexes.

Mean amplitudes of S waves in V and R waves in V and V were significantly greater in men than in women and in Africans than Indians. These differences could only be partially explained by variations in age blood pressure obesity or cardiothoracic ratios.

Possible ethnic and sex differences in the prevalence of T wave inversion in right precordial leads, S-T elevation and high amplitude QRS complexes can be of clinical and epidemiological importance

We are grateful to the Guyana Sugar Producers Association for allowing us the use of their facilities, to Mrs V Beadnell electrocardiographer and to Dr C du V Florey for statistical help.

REFERENCES

1 Littman, D Persistence of the juvenile pattern in precordial leads of healthy adult Negroes, with report of an electrocardiographic survey on 300 Negro and 200 Caucasian subjects, Amer Heart J 32 370 1946.
2. Walker A R P and Walker B F The bearing of race, sex age and nutritional status on the precordial electrocardiograms of young South African Bantu and Caucasian subjects, Amer. Heart J 77:441 1969
3. Ashcroft, M. T Beadnell, H. M S. G., Bell R., and Miller G. J Characteristics relevant to cardiovascular disease among adults of African and East Indian origin I Guyana, Bull. W.H.O 42:205 1970.
4. Ashcroft, M T Beadnell, H. M. S G Miller G. J and Bell, R. Anthropometric measurement of Guyanese adults of African and East Indian racial origins, Trop. Geogr Med. 1 169 1969
5. Simonson, E. Differentiation between normal and abnormal in electrocardiography St. Louis, 1961 The C. V. Mosby Company
6 Gottschalk, C. W and Craige E. A comparison of the precordial S-T and T waves in the electrocardiograms of 600 healthy young Negro and White adults, Southern Med. J 49 453 1956.
7 Brink, A. J The normal electrocardiogram in the adult South Africa Bantu, S. Afr. J Lab. Clin. Med. 2:97 1956.
8. Grusin, H Peculiarities of the African electrocardiogram and the changes observed in serial studies, Circulation 9:860, 1954
9 Goldman, M J RS-T segment elevation in mid and left-precordial leads normal variant, Amer Heart J 46:517 1953
10. Thomas, J Harris E., and Lassiter G Observations on the T wave and S-T segment changes in the precordial electrocardiograms of 320 young Negro adults, Amer J Cardiol 5:468 1960
11 Wasburger R. H and Alt, W J The normal RS-T segment elevation variant, Amer J Cardiol. 8 184 1961
12. Pyke D A. Electrocardiographic changes in West Indians, Proc. Roy Soc. Med. 56:567 1963
13 Powell, S. J Unexplained electrocardiograms in the African, Brit. Heart J 21:263 1959
14 Somers, K., and Rankin, A. M The electrocardiogram in healthy East Africans (Bantu and Nilotic) men Brit. Heart J 24:542 1962.
15 Seriki, O and Smith, A. J The electrocardiogram of young Nigerians, Amer. Heart J 72:153 1966.
16. Dharmadasa, K., and Nadarajah, M Electrocardiograms in young Ceylonese Brit. Heart J 30 765 1968.
17 Srikantia, S. G., Padmavati, S., and Gopalan C. The electrocardiogram in some Indian population groups, Circulation 29 118 1964
18. Rose, G. A., and Blackburn, H Cardiovascular survey methods, W.H.O Monograph Series, No. 56 1968.
19 Goldman, M J Normal variants in electrocardiograms leading to cardiac invalidism Amer. Heart J 59 71 1960.
20. Romhilt, D W Bove, K. E., Norris, R. J Conyers, E Conradi, S Rowlands, D. T and Scott, R. C. A critical appraisal of the electrocardiographic criteria for the diagnosis of left ventricular hypertrophy Circulation 40 185 1969

occurring whenever J is situated above the isoelectric line and sometimes the criteria have required, as in this study, that the S-T segment should be concave. Using the former definition, S-T elevation tends to be more prevalent in right precordial leads when J is situated on the rising limb of an S wave; using the latter definition, S-T elevation is seen more often in leads further to the left, when J is placed on the descending limb of an R wave. Investigators, however, are agreed that the prevalence of S-T elevation of one kind or another is unexpectedly high in subjects of African origin both in the New World[4, 9, 12] and in Africa.[2, 7, 8, 13, 15] No studies on S-T elevation in India have been traced but healthy men in Ceylon[16] have been found to have a high prevalence.

Most investigations have revealed that QRS complexes in precordial leads are of greater amplitude in healthy Africans than in Caucasian subjects.[2, 7, 8, 13, 15] Ceylonese[16] and Indians[17] also have R waves of higher amplitudes than expected by generally accepted Caucasian standards. The Guyanese data confirm the frequency of S-T elevation and the high amplitude of R and S waves in Africans and, to a lesser extent, in Indians. The association between S-T elevation and large R and S waves (Table IV) suggests that the greater prevalence in Africans than in Indians or Caucasians and in men than in women may be influenced by the relative size of the QRS complexes. There is no evidence to suggest that S-T elevation was abnormal (Table IV).

Sex and ethnic differences in ECG patterns can be of importance both in epidemiological surveys and in clinical practice. Many community surveys involving the recording of ECG's have been undertaken in recent years and the results have often been recorded by the Minnesota Code.[18] In precordial leads the coding 5 2 refers to negative or diphasic T waves with a negative phase at least 1.0 mm. in Leads V_2, V_3, V_4, V_5, or V_6. The code 5 3 is given if T is flat, negative, or diphasic with a negative phase of less than 1.0 mm. in Leads V_2, V_4, V_5, or V_6. (In the present investigation the negative phase was taken as 0.5 mm. rather than 1.0 mm. as used in the code.)

In the Guyana survey, using the Minnesota Code, 2 men and 11 women had codable T wave changes in V_1, V_2, and V_3, changes not being found in any other lead. A typical example is shown by ECG No. 545 in Fig. 1. Characteristics such as blood pressure, skinfold thickness, and serum cholesterol were similar in these subjects to those with normal ECG's.[3] The same characteristics of 19 African and 18 Indian women with nonupright (not all codable) T waves in V_2 and V_3 did not differ significantly from those of subjects with upright T waves (Table II). This evidence suggests that at least in the majority of cases nonupright or inverted T waves in V_2 and V_3 in women were not associated with ischemic heart disease or hypertension and were a normal variant. T wave inversion in V_2 and V_3 in men was not seen, a finding in agreement with another survey of Negro subjects in America[9] but, for unexplained reasons, T wave inversion in these leads in healthy Africans has been found to be more common.[2, 7, 8, 13] Unless allowance is made for the occurrence of this pattern as a normal variant in women and in subjects in Africa, then comparisons, using the Minnesota Code, of different ECG surveys might be misleading.

Cardiologists today are cautious of diagnosing pathological conditions of the heart from the presence of T wave inversion in right precordial leads alone and of S-T elevation without additional evidence of abnormalities in other leads or on clinical examination. In the past, however, unnecessary cardiac invalidism sometimes resulted from a lack of awareness that these patterns, which can resemble the patterns found in pericarditis or myocardial infarction, may be normal.[9]

Many of the indices which are commonly used for left ventricular hypertrophy depend on the amplitude of the S wave in V_1 and R waves in V_5 or V_6. In a recent study 33 different criteria were evaluated against autopsy findings utilizing chamber dissection techniques.[19] The greatest sensitivity (56 per cent) was given by 5 criteria, all of which were based on the sum of various combinations of R- and S-wave amplitudes in precordial leads. Although any criterion for LVH based on wave amplitude is only an approximation, the

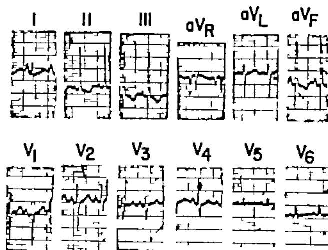


Fig 1 ECG P tient 1

The -ray showed the cardiac shadow t be enlarged in the transverse diameter with large right atrium and an uptilted pex. The vascularity as markedly decreased.

These findings suggested that the infant had pulmonary atresia with an intact septum and immediate arrangements ere made for surgery at nother hospital.

An operation as performed at 29 hours of age. A Brock pulmonary valvulotomy as done Because there as no appreciable improvement, Pott procedure was then done. A ductus arteriosus which as adding very little to the pulmonary flow was ligated. At the conclusion of surgery blood gas stud ies revealed pH of 7 4, Pa_{CO_2} 31 mm. Hg and oxygen saturation 81 per cent At this time the infant was digitalized.

The following day (second postoperative day) the infant appeared pink and alert and assisted respira tion as discontinued. A grade 2/6 blowing systolic murmur was now heard in the pulmonic area, but no diastolic murmur was udible.

Not until the ninth postoperative day was shunt murmur heard in the left infraclavicular area for the first time. This then remained as constant finding.

Cardiac catheterization and angiography were performed on the fifteth postoperative day The right ventricular pressure was 120/13 The angiograms showed right ventricle of moderate size with an irregular outflow tract and deformed pulmonary valve there was slight tricuspid regurgitation.

The infant was discharged on the fifty-second postoperative day in satisfactory condition, mild cyanosis being noted only with severe crying

Patient 2 J S male infant, was admitted at the ge of 2 days. Cyanosis and systolic murmur had been noted shortly after birth at another hospital. The baby eighed 3,520 grams t birth, was active, and had good cry Although there was no respiratory distress, it was noted that the cyanosis was becoming progressively orse, especially with crying, and the infant was transferred.



Fig 2 X-ray Patient 2.

Shortly after arrival he was noted to be deeply cyanotic. The heart rate was 120/min. and regular There was grade 3/6 blowing holosystolic murmur maximum low down along the left sternal border transmitted to right and left but not to the base. The second sound at the pulmonic area was equal to the second sound at the aortic area and was probably single. The lungs were clear Liver and spleen were not enlarged. Chest roentgenogram (Fig. 2) showed transversely enlarged heart with large right atrium and uplifted apex. The vascularity

Pulmonary atresia with intact interventricular septum operative treatment with survival

*George D Rook M D F.A A P**

*Norman Gootman M D F A A.P***

New York N Y

Pulmonary atresia with intact septum has been defined as a condition which consists of complete obstruction of the pulmonary valve 2 distinct ventricles and a patent tricuspid orifice guarded by a valve[1]

It has been considered a relatively uncommon lesion[1,2] Keith[2] includes 68 cases in his chapter on pulmonary atresia with intact septum and calculates that it makes up about 1 per cent of all congenital heart lesions A recent review of the literature disclosed 123 reported cases[4] Of this entire group only three survived following operative treatment

This lesion has been subjected to much anatomic study It has been subdivided further depending on the size of the right ventricle Type I with a small right ventricle making up about 80 per cent of the cases and Type II with a large or normal right ventricle the remaining 20 per cent It has been pointed out that the distinction between the 2 types is not always clear and there may be an entire spectrum from small to large right ventricles[4] An attempt has been made to differentiate the 2 types by electrocardiography and it has often been stated that only Type II with a large right ventricle is amenable to surgery

It is the purpose of this paper to report 3 additional cases of pulmonary atresia with intact interventricular septum seen over a comparatively short period of time. These cases are of interest because the infants survived after prompt surgery and because of the electrocardiograms which would have been according to the literature a contraindication for surgery

Case reports

Patient 1 D T a 2800 gram female infant was delivered from a 24-year-old primagravida by cesarean section. The Apgar score at 5 minutes was 9 However general cyanosis became apparent at 4 hours of age and at that time a systolic murmur was heard. The cyanosis became progressively worse and the infant had several apneic spells. At 22 hours of age auscultation revealed a grade 2/6 blowing holosystolic murmur at the lower left sternal border There was a systolic ejection click over the second and third right intercostal spaces and the second sound over the pulmonic area was decreased in relation to the second sound in the aortic area. The rhythm was regular The lungs were clear The liver and spleen were not enlarged. All pulses were easily palpable and equal. The electrocardiogram (ECG) (Fig 1) showed regular sinus rhythm a frontal QRS axis of +80 degrees peaked 3 mm P waves one there was no R in aVR R/S ratio in V_1 of 5/12 3 mm. R in V without an S The interpretation was right atrial hypertrophy and left ventricular preponderance

From the Pediatric Service, Long Island Jewish Hospital, New York, N Y

Received for publication May 27 1970.

Reprint requests to Dr George Rook, Department of Pediatrics, New York Medical College-Metropolitan Hospital, 1901 First Avenue, New York, N Y 10029

*Dr George Rook, Associate Professor of Pediatrics, New York Medical College.

**Dr Norman Gootman, Assistant Clinical Professor of Pediatrics, Downstate Medical College.

April 1971 Vol. 81 No. 4 476-481

discharged on the thirty-second postoperative day. Blood studies shortly before discharge showed an oxygen saturation of 85 per cent, PaO_2 of 54 mm. Hg, and pH of 7.38.

Patient 3 R. P. 3080 gram male inf t was delivered to 36-year-old mother uneventfully t another hospital following normal pregnancy. The Apgar score was 9 at 1 minute.

At 3 hours of age the infant was noted to be cyanotic and tachypneic. On examination the heart rate as 160/minute and regular; no second sound as heard in the second to third left intercostal spaces; there was no murmur. All pulses ere normal. The rest of the physical exam was negative.

X-ray showed slight increase in the transverse diameter of the heart; the pulmonary vascularity as definitely decreased. ECG (Fig. 4) showed frontal axis of +30 degrees, no R in V₁, and R in V of 15 mm. ith an S of 2 mm. suggesting left ventricular hypertrophy. P waves were 3 mm. and peaked in Lead II.

The infant was transferred on the second day of lif and cardiac catheterization and angiography ere performed.

The important findings were O_2 saturations of less than 20 per cent on the right side of the heart nd 30 per cent in the right femoral artery. The right ventricular pressure was 77/10 and the femoral artery pressure 90/42.

Cine angiography i posteroanterior and lateral projections showed pulmonary valv tresia th intact ventricular septum nd an adequate right entricle.

A Brock procedure was performed and the arterial oxygen saturation immediately rose to 77 per cent. However 18 hours later it had fallen to 16 per cent. At this time murmur suggesting tricuspid regurgitation as heard. The child as again taken to the operating room and Pott procedure was done. The arterial oxygen saturation again rose to over 80 per cent. The postoperative course was uneventf l except for left telectasis and pneumonitis which cleared slowly.

The infant was discharged on the twenty-ninth postoperative day.

Discussion

These 3 cases demonstrate many of the findings previously described in articles on pulmonary atresia with intact interventricular septum.

All reports (1 to 9) describe early cyanosis, usually severe and progressive. Anoxic spells are frequent and often the cause of death. Dyspnea is absent unless congestive heart failure supervenes. This may occur in up to 50 per cent of the cases.[4,6,11] The finding of a thrill is unusual, Davignon[5] being one of the rare authors mentioning this finding in 2 of his 16 cases. Both these cases had a large right ventricle.

Although Rowe and Mehrizi state that the blowing systolic murmur maximal along the lower left sternal border characteristic of tricuspid regurgitation is only occasionally heard and Edwards and associates[1] concur most authors with large series[2-4,7,10] have found this murmur in the majority of their cases. It can be heard in patients with either large or small right ventricles. Patients 1 and 2 of this report had the characteristic regurgitant murmur from birth while Patient 3 developed it postoperatively. Ejection murmurs and murmurs of patent ductus arteriosus have also been reported.[3,4-10] The second sound in the pulmonic area is usually decreased and single.

All 3 cases in this report had very similar roentgenograms. The hearts were enlarged with large right atria, horizontal extension of apices and concave pulmonary artery segments giving the over all impression of a football lying on the ground. The pulmonary vascular markings were greatly diminished. Angiography is the most satisfactory procedure for making the diagnosis. If possible the injection should be made into the right ventricle. This will show the atretic valve and the myocardial sinusoids which may anastomose with the coronary circulation. If the right ventricle cannot be entered, then the injection is made into the right atrium. This may fill the ventricle but at times the contrast medium will pass directly into the left atrium. A diagnosis of tricuspid atresia can be avoided by noting the manner in which the pulmonary artery fills. In pulmonary atresia it can fill only retrograde through a patent ductus while in tricuspid atresia it fills from below through a ventricular septal defect. Both conditions show large right atria and poor flow to the lungs.

The electrocardiogram has been considered one of the most important diagnostic tools in differentiating pulmonary atresia with intact septum from other forms of cyanotic heart disease. The characteristic ECG has been described as showing right or normal axis deviation, right atrial hypertrophy and left ventricular hypertrophy. However many authors[3,4,7-9,11] have described variations from this pattern. At

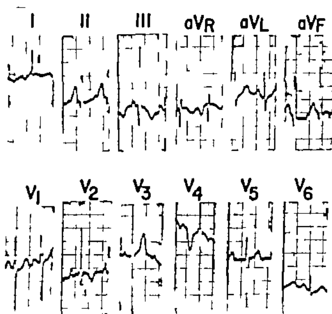


Fig 3 ECG Patient 2

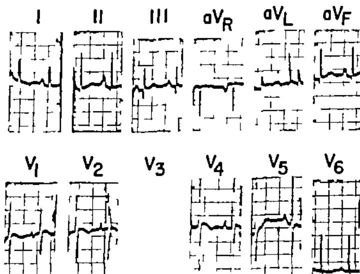


Fig 4 ECG Patient 3

wa markedly decreased The electrocard ogram (F g 3) showed n a is more to the left than expected at this age (+60) there w a 1 mm S w e nd a 5 n m R wave in V_4 R/S tlo V wa 11/15 I waves in Leads II V nd V_4 were h gh nd peaked and the T waves were normal for the ge These f nd ngs were nterpreted show ng right atrial enlargement nd left ventricular enlargement

On cardiac catheterization the following oxygen saturat ons were found right atrium and right ventricle, 30 per cent left atrium 43 per cent pul monary vein, 91 per cent and femor l artery 53 per cent The pressures were right entricula 86/3 right femoral artery 84/50

A biplane cardioang ogram was done from the right atrium This revealed a large right atrium and good sized right ventricle. Both the right ventricle and left atrium filled immediately The outflow tract of the right ventricle was somewhat d lated and nded abrupt ly in the valv lar are The left atrium, left ventricle and aort were normal and filled in sequence The p lmonary arteries which were of good size then f lled through pate t duct

The inf t wa taken to the operat ng room. A v lvul tome w p sed through a opening in the right e tricle just prox mal t the outflow tract nd the membrane form ng the pulmonary val e was opened There w immediate marked improvement in the f t s color

At the termination of the oper tion the nfant was digitalized

The murmur of tricu pid reg rgitation changed l ttle postoperat vely nd a Grade 2-3/6 p lmonic ejection m rmur was also heard There w no diastolic murm ur The hospital course was unevent ful except for an aspiration pneumonia. He was

discharged on the thirty-second postoperative day. Blood studies shortly before discharge showed oxygen saturation of 85 per cent, PaO_2 of 54 mm. Hg, and pH of 7.38.

Patient 3. R. P., a 3050 gram male infant, was delivered to a 36-year-old mother uneventfully at another hospital following a normal pregnancy. The Apgar score was 9 at 1 minute.

At 3 hours of age the infant was noted to be cyanotic and tachypneic. On examination the heart rate was 160/minute and regular; no second sound was heard in the second to third left intercostal spaces; there was no murmur. All pulses were normal. The rest of the physical exam was negative.

X-ray showed a slight increase in the transverse diameter of the heart; the pulmonary vascularity was definitely decreased. ECG (Fig. 4) showed a frontal axis of +30 degrees, no R in V_{4R}, and an R in V_6 of 15 mm. with an S of 2 mm. suggesting left ventricular hypertrophy. P waves were 3 mm. and peaked in Lead II.

The infant was transferred on the second day of life and cardiac catheterization and angiography were performed.

The important findings were O_2 saturations of less than 20 per cent on the right side of the heart and 30 per cent in the right femoral artery. The right ventricular pressure was 77/10 and the femoral artery pressure 90/42.

Cine angiography in posteroanterior and lateral projections showed a pulmonary valve atresia with intact ventricular septum and an adequate right ventricle.

A Brock procedure was performed and the arterial oxygen saturation immediately rose to 77 per cent. However, 18 hours later it had fallen to 16 per cent. At this time a murmur suggesting tricuspid regurgitation was heard. The child was again taken to the operating room and a Potts procedure was done. The arterial oxygen saturation again rose to over 80 per cent. The postoperative course was uneventful except for a left atelectasis and pneumonitis which cleared slowly.

The infant was discharged on the twenty-ninth postoperative day.

Discussion

These 3 cases demonstrate many of the findings previously described in articles on pulmonary atresia with intact interventricular septum.

All reports (1 to 9) describe early cyanosis, usually severe and progressive. Anoxic spells are frequent and often the cause of death. Dyspnea is absent unless congestive heart failure supervenes. This may occur in up to 50 per cent of the cases.[4,10] The finding of a thrill is unusual, Davignon[3] being one of the rare authors mentioning this finding in 2 of his 16 cases. Both these cases had a large right ventricle.

Although Rowe and Mehrizi[?] state that the blowing systolic murmur maximal along the lower left sternal border characteristic of tricuspid regurgitation is only occasionally heard and Edwards and associates[1] concur, most authors with large series[3-5, 8,9] have found this murmur in the majority of their cases. It can be heard in patients with either large or small right ventricles. Patients 1 and 2 of this report had the characteristic regurgitant murmur from birth while Patient 3 developed it postoperatively. Ejection murmurs and murmurs of patent ductus arteriosus have also been reported.[4,5] The second sound in the pulmonic area is usually decreased and single.

All 3 cases in this report had very similar roentgenograms. The hearts were enlarged with large right atria, horizontal extension of apices, and concave pulmonary artery segments giving the over all impression of a football lying on the ground. The pulmonary vascular markings were greatly diminished. Angiography is the most satisfactory procedure for making the diagnosis. If possible the injection should be made into the right ventricle. This will show the atretic valve and the myocardial sinusoids which may anastomose with the coronary circulation. If the right ventricle cannot be entered, then the injection is made into the right atrium. This may fill the ventricle but at times the contrast medium will pass directly into the left atrium. A diagnosis of tricuspid atresia can be avoided by noting the manner in which the pulmonary artery fills. In pulmonary atresia it can fill only retrograde through a patent ductus while in tricuspid atresia it fills from below through a ventricular septal defect. Both conditions show large right atria and poor flow to the lungs.

The electrocardiogram has been considered one of the most important diagnostic tools in differentiating pulmonary atresia with intact septum from other forms of cyanotic heart disease. The characteristic ECG has been described as showing right or normal axis deviation, right atrial hypertrophy, and left ventricular hypertrophy. However, many authors[3-5, 8,10,11] have described variations from this pattern. At

tempts have been made to correlate these variations of the ECG with the size of the right ventricle because it is believed this factor is the determinant when surgery is contemplated Keith[3] states that since there is an entire spectrum of right ventricular size in this entity rather than a division into 2 types prediction on the basis of an ECG is unreliable except for the extremes if there is gross ventricular hypertrophy with clinical evidence of tricuspid regurgitation there will be right ventricular hypertrophy (RVH) while if the right ventricular cavity is minute there will be left ventricular hypertrophy (LVH) Cole and co workers[10] and Gersony and associates[4] also believe the ECG is not a completely reliable indicator of right ventricular size

The 3 cases described in this report all showed the characteristic findings of normal axis deviation right atrial hypertrophy and left ventricular hypertrophy Yet all three had evidence of tricuspid regurgitation and showed an adequate right ventricle on angiographic study All three survived operation

Only with surgical intervention can children with this entity avoid early death Even with early surgery there have been very few survivors[3,4,6,7,9,11] The ideal management is early study to determine the configuration of the right ventricular outflow tract and the size of the right ventricle main pulmonary artery and interatrial communication and then immediate appropriate surgery

The outcome seems to depend to a large extent on the adequacy of the right ventricle as a pumping chamber Until very recently a small right ventricle was considered a contraindication to surgery[4] At present because of the hopeless prognosis without operation a number of procedures have been suggested[3,4,8,10] From experience with the three cases reported above and a review of the literature it is believed that appropriate surgery should consist first of a Brock procedure If the right ventricle is adequate this may be all that is needed It will also help decompress this ventricle even if it should prove incapable of maintaining satisfactory cardiac output. If this should be the case, either a Potts or Waterston procedure should follow If such a shunt is necessary then in addition creation of an adequate interatrial communication may be required to permit adequate right to left flow at the atrial level There are a number of implications raised when the literature on pulmonary atresia with intact interventricular septum is viewed in the light of the 3 cases presented here

First Infants with this lesion must be handled expeditiously Diagnostic studies should be undertaken at once and surgical correction should follow without delay if there is to be any hope of survival

Second Infants showing left ventricular hypertrophy on the electrocardiogram may have a right ventricle of adequate size and be more amenable to surgery than has previously been considered

Third Even in cases demonstrating a small right ventricle on angiography surgery offers the only chance for survival Here a combination of operations including a Brock some type of aortopulmonary shunt and enlargement of the interatrial communication may be necessary

Summary

A recent review of the literature found 123 cases of pulmonary atresia with intact interventricular septum This report adds three more cases

It is suggested that immediate diagnostic studies followed by surgery may improve the chances of survival in a condition which has had a mortality rate approaching 100 per cent

The patients reported here are now 2 years 4 months ? years 2 months and 1 year 4 months of age and doing well

REFERENCES

1 Edwards, J E Carey L S Neufeld H N and Lester R G Congenital heart disease, Vol. 2 Philadelphia 1965 W B Saunders Compa y p. 575
Elli tt, L P Adams, P Jr and Edwards, J E. Pulm nary atresia with intact ventricular septum Brit Heart J 25:489 1963
3 Keith J D Rowe R D and Vlad P Heart disease in infancy and childhood ed. 2 N Y 1967 The Macm llan Company
4 Gersony W E. Bernhard W F Nadas, A. S. and Gross, R. E. Diagnosis and surgical treatment of inf ts with critical pulmonary outflow obstruction, Circulation 35 765 1967

5. Davignon, A. L., Greenwold W. E., DuShane, J. W. and Edwards, J. E. Congenital pulmonary atresia with intact ventricular septum clinico—Pathologic correlation of two anatomic types, Amer. Heart J 62:591 1961
6. Lambert, E. C., Tingelstad, J B and Horn, A. R. Diagnosis and management of congenital heart disease in the first week of life Pediat. Clin. N Amer 13:943, 1966.
7. Benton, J W J Elliott, L. P Adams, P J Anderson, R. C., Hong C. Y and Lester R. G. Pulmonary atresia and stenosis with intact ventricular septum Amer J Dis. Child. 104 161, 1962.
8. Kiely B., Morales, F and Rosenblum D Pulmonary atresia with intact ventricular septum, Pediatrics 32:841 1963.
9. Rowe, R. D and Mehrizi, A. The neonate with congenital heart disease, Philadelphia 1968, W B. Saunders Company p. 211.
10. Cole R. B., Muster A. S., Lev M and Paul M H. Pulmonary atresia with intact ventricular septum, Amer J Cardiol. 21:23 1968.
11. Gamboa, R., Gersony W M and Nadas, A. S. ECG in tricuspid atresia and pulmonary atresia with intact ventricular septum Circulation 34:24 1966.
12. Ziegler R. F and Taber R. E. Diagnostic criteria and successful surgery in an operable form of complete pulmonary valve atresia, Circulation 26:807 1962. (Abst.)

The effect of clonidine on hemodynamics in hypertensive patients

Donald R McRaven M D
Frank H Kroetz M D
J Michael Kioschos M D
Walter M Kirkendall M.D
Iowa City Iowa

The imidazoline derivative (2 [2 6 dichlorophenylamino] imidazoline hydrochloride) ST 155 generic name clonidine lowers arterial pressure in animals and man It is chemically unrelated to any established antihypertensive drug

Clonidine produces bradycardia and a biphasic blood pressure response characterized by an initial brief rise in arterial pressure followed by a prolonged reduction of pressure[1,2] The pressor effect in animals is caused by direct stimulation of alpha adrenergic receptors[3-4] The depressor effect has been related to inhibition of sympathetic centers in the brain stem which result in decreased sympathetic activity to the heart and vascular bed[4,5] Various investigators have found that the reduction of cardiac output contributes to the lowering of blood pressure[6,7] Clonidine is reported to have little direct or reflex effect on myocardial function[8] but decreased sympathetic stimulation to the heart is thought to account for its bradycardic effect[8] The effect of clonidine on resistance vessels remains controversial Total systemic resistance has been reported to be decreased or unchanged[8,9,10] In dogs on total heart lung bypass and constant cardiac output blood pressure was lowered by clonidine indicating increased systemic vascular resistance in that preparation[4,11]

This study was done to further assess the acute hemodynamic effects of clonidine in patients with hypertension

Materials and methods

Patients Table I summarizes the clinical information of the 8 patients studied Ages ranged from 28 to 63 6 were men and 2 were women At the time of the study none of our patients had severe hypertension and 3 had diastolic pressures below 90 mm Hg although all were noted previously to have sustained elevation of blood pressure Duration of documented hypertension was 2 weeks to over 20 years. Five patients had essential hypertension and 3 had renal disease with hypertension Patients received no antihypertensive drugs for at least 9 days prior to the study except R N who received chlorothiazide until the day of the study

Methods Patients were studied as in patients in the fasting state and without premedication All measurements were made in the supine position Continuous electrocardiographic monitoring was done

From the Cardiovascular Research Laboratories, Department of Internal Medicine University of Iowa College of Medicine Iowa City Iowa 52240.

Received for publication June 8, 1970.

Reprint requests to Dr Donald R. McRaven, 2722 West Oklahoma Ave Milwaukee Wis. 53215.

Table I Patients studied with arterial hypertension

Initials	Age	Sex	Ht./wt.	BSA	Duration of documented hypertension	Etiology
R. C.	49	F	65/119	1 58	8 yr	Associated with congenital hydronephrosis
H. H.	28	M	69/184	2 00	3 yr	Essential
R. N	42	M	68/173	1 94	5 y	Essential
D. L.	56	F	63/191	1 86	20 yr	Associated with chronic renal disease
H. B.	57	M	68/154	1 83	3 yr	Essential
S. H.	36	M	70/178	1 99	2 yr	Essential
F. B	63	M	61/102	1 42	2 wk.	Essential
W. W	59	M	70/186	2 02	17 wk.	Chronic glomerulonephritis

Ht. = Height in inches, wt. = weight in pounds, BSA = body surface area in square meters.

Right heart catheterization from a superficial right antecubital vein was done. Pressures were measured from the right atrium right ventricle pulmonary artery and pulmonary artery wedge positions. Intra-arterial pressure was monitored through a Cournand needle placed percutaneously into a brachial artery Cardiac outputs were obtained by dye dilution technique using indocyanine green dye and a cuvette densitometer Oxygen consumption was determined in the standard fashion by analysis of the oxygen content of expired air using a Beckman Model E oximeter Left ventricular ejection was determined by analysis of the indirect carotid pulse and the Q-S_1 interval from an electrocardiogram and phonocardiogram All recordings were made by an Electronics for Medicine recorder

Measurements first were made in the basal state. Clonidine 150 μg was given intravenously over two and a half minutes. The blood pressure response stabilized in 10 to 20 min. and all measurements were then repeated A second dose of 150 μg was given about 30 min after the first. Again blood pressure response stabilized in 10 to 20 min and all measurements were repeated.

Following completion of the study patients were returned to their rooms and supine blood pressures were measured every 30 min until the prestudy levels returned.

Statistical methods Data were analyzed by Student t test using paired data The level of significance chosen for this study was a $p < 0.05$ The effects following 150 μg of clonidine were compared to control and the effects following 300 μg of clonidine with those at control and after 150 μg Responses after 300 μg are discussed in comparison to the responses after 150 μg except for heart rate which is compared to control

Results

Results are given in Tables II III and IV

Effects on systemic pressure and resistance Infusion of 150 μg of clonidine produced an initial pressor response in 5 of the 8 patients. Maximum pressures were observed 10 to 40 sec. after injection. Arterial pressure always returned to control level by two and a half minutes. The average duration of the pressor response was 1.3 min. The greatest response was observed in D L. in whom arterial pressures rose from 156/73 to 200/117 mm. Hg The average blood pressure rise was 26 mm. Hg (14 per cent) systolic pressure and 16 mm Hg (17 per cent) diastolic pressure.

Systolic and mean arterial pressure quickly fell in all patients. Diastolic pressure fell in 7 of 8 Systolic pressure was reduced 19 per cent (from 196 to 159 mm Hg) ($p < 0.02$) diastolic pressure 16 per cent (from 101 to 85 mm Hg) ($p < 0.01$) and mean pressure 17 per cent (from 135 to 110 mm. Hg) ($p < 0.01$) Additional reductions in arterial pressure after a second dose of 150 μg or a total dose of 300 μg were significant only for systolic pressure which

fell to 145 mm Hg or 28 per cent Diastolic pressure fell to 78 mm Hg or 23 per cent and mean pressure fell to 99 mm Hg or 27 per cent.

The total systemic resistance was unchanged at both dose levels

Effects on cardiac output The cardiac index fell in all patients after 150 μg clonidine averaging 16 per cent ($p < 0.01$) The further reduction in cardiac index to 24 per cent below control after a total dose of 300 μg was not significant.

Effects on heart rate Changes in heart rate after 150 μg were variable and not significant Slight slowing of heart rate from 81 to 76 beats per minute ($p < 0.05$) occurred after 300 μg

Effects on pulmonary artery pressure and

Table II *Initial pressor responses to clonidine*

Patient	150 μg					300 μg				
	Arterial pressure (mm Hg)				Duration (min)	Arterial pressure (mm Hg)				Duration (min)
	Control	Maximum	Change			Control	Maximum	Change		
			Actual	%				Actual	%	
R. C.	222/106	234/114	12/8	5/8	1 0	172/92	191/104	19/12	11/13	1 0
R. N	142/85	184/117	42/32	30/38	0 5	168/96	181/117	13/21	8/22	0 5
D L.	183/83	223/99	40/16	21/19	2 5	156/73	200/89	44/16	28/22	2 0
F B	242/136	262/146	20 10	8/7	1 0	202/107	222/117	20/10	10/9	1 5
W W	155/74	187/93	32/19	21/26	2 0	150/74	167/85	17/11	11/15	1 0
Mean	189/96	218/113	29/17	15/18	1 4	170/88	192/102	22/14	13/16	1 2
Combined average for both doses			26/16	14/17	1 3					

Table III *Hemodynamic response to intravenous administration of 150 μg and 300 μg clonidine*

Initials	CI			HR			SVI			pO2		
	c	150	300	c	150	300	c	150	300	c	150	300
R. C.	3 29	2 65	2 18	91	95	88	36	25	25	178	141	134
H. H.	3 31	3 05	2 42	67	83	79	49	37	31	332	331	314
R. N	2 68	2 33	1 84	87	71	77	31	33	24	—	—	—
D L.	2 77	2 04	2 31	80	74	64	35	25	37	262	233	203
H. G.	2 75	1 90	1 90	87	85	84	32	22	24	225	191	153
S. H.	2 41	2 14	1 85	58	65	52	42	33	36	293	219	—
F B.	2 00	1 70	1 50	96	93	86	21	18	17	203	191	137
W W	3 02	2 68	2 66	85	85	79	36	32	34	263	223	179
M	2 78	2 31	2 10	81	81	76	35	29	29	252	221	193
Standard deviation	0 44	0 45	0 38	13	11	12	8	6	7	63	60	75
P value versus control		<0 001	<0 001	—	—	—	—	<0 01	<0 02	—	<0 01	<0 05
P value versus 150		—	—	—	—	<0 05	—	—	—	—	—	—

Abbreviations: c = control; 150 = after 150 μg clonidine; 300 = after 300 μg clonidine CI = cardiac index (liters per minute per square meter) HR = heart rate (beats per minute) SVI = stroke volume index (milliliters per square meter) qO_2 = rate of oxygen consumption (cubic centimeters per minute); AP = arterial pressure; S = systolic (millimeters hemoglobin) D = diastolic (millimeters hemoglobin); M = mean (millimeters hemoglobin); MPA = main pulmonary pressure (millimeters hemoglobi MPAW = mean pulmonary artery edge pressure (millimeters hemoglobin); MRA = mean right atrial pressure (millimeters hemoglobin)

resistance Serial observations of mean pulmonary artery pressure were made in 5 patients. Mean pulmonary artery pressure *fell slightly* after 150 µg from 17 to 15 mm. Hg ($p < 0.05$) Further reduction to 13 mm. Hg occurred after a total dose of 300 µg ($p < 0.05$)

The total pulmonary resistance and pulmonary arteriolar resistance were unchanged.

Effects on left ventricular minute-work index ejection index systolic intervals and tension-time index After 150 µg of clonidine left ventricular minute-work index fell from 5.8 to 4.1 Kg. M. per square meter ($p < 0.001$) Further significant reduction to 3.3 Kg M per square meter ($p < 0.05$) occurred after 300 µg. Left ventricular stroke work index fell from 73 to 50 Gm. M. per square meter per second ($p < 0.01$) after 150 µg with no additional significant change after the second dose.

Mean rate of left ventricular ejection index fell from 140 to 120 ml. per square meter per second ($p < 0.01$) after 150 µg with little further change after the second dose.

Study of the systolic intervals revealed that the duration of electrical mechanical systole measured by the Q-S_2 interval was unchanged after 150 µg and after 300 µg. Left ventricular ejection time was also essentially unchanged. However the pre ejection period (Q-S_2 interval to left ventricular ejection time) was slightly prolonged after 150 µg from 0.109 to 0.119 sec. ($p < 0.001$) No further change in pre-ejection period occurred after the total dose was increased to 300 µg

Arterial pressure–time product (tension-time index) fell from 3,255 to 2,702 mm. Hg seconds per minute ($p < 0.01$) Further reduction after the second dose of clonidine was not significant.

Effects on filling pressures Mean pulmonary artery wedge pressure a reflection of left ventricular filling pressure fell from 9 to 6 mm. Hg ($p < 0.05$) after 150 µg with no further change after the second dose. Right atrial mean pressure tended to fall but the change was not significant.

Effects on oxygen consumption. Oxygen consumption was reduced from 252 to 221 c.c. per minute ($p < 0.01$) after 150 µg. Further reduction to 193 c.c. per minute occurred after a total dose of 300 µg. This change from the initial response was not significant.

General effects All patients experienced drowsiness during the study. Drowsiness

AP S/D (M)			MPA			MPAW			MRA		
	150	300		150	300		150	300		150	300
221/109(154)	179/96(123)	162/87(113)	13	10	10	7	6	5	3	3	2
199/119(141)	170/101(130)	196/90(115)	15	13	10	6	6	8	4	4	3
181/95(125)	151/77(99)	122/75(91)	—	—	—	—			4	3	2
192/83(120)	144/77(91)	142/87(87)	16	—	—	—			3	3	4
224/102(145)	142/71(91)	174/87(108)	26	21	18	12	9	9	8	6	6
136/86(110)	125/80(91)	107/87(78)	15	13	11	11	5	6	5	4	3
202/138(172)	200/106(140)	182/90(107)	—	—	—	—			2	3	3
171/103(120)	144/84(105)	128/70(86)	15	13	14	8	7	7	6	7	6
194/103(130)	140/84(110)	143/73(99)	17	15	12	9	6	6	4	4	3
31/20(22)	24/14(21)	24/13(14)	6	5	3	2	1	2	3	3	2
—	<0.02/<0.01(<0.01)	<0.01/<0.01(<0.001)	—	<0.05	<0.01	—	<0.05	<0.02			
—	—	<0.05/ ( )	—	—	<0.05	—					

Table IV. Hemodynamic response to intravenous administration of 150 µg and 300 µg clonidine

Initials	Q – S₂			LVET			PEP			TSR			PAR		
	c	150	300	c	150	300	c	150	150	c	150	300	c	150	300
R. C	0.368	0.303	0.376	0.274	0.202	0.259	0.091	0.100	0.118	2372	2356	2023	93	76	114
H. H	0.396	0.363	0.374	0.272	0.238	0.231	0.121	0.135	0.140	1738	1700	1909	72	83	83
R. N	0.374	0.396	0.373	0.249	0.248	0.220	0.125	0.138	0.144	1571	1702	2031	—	—	—
D. L.	0.343	0.318	0.379	0.250	0.231	0.278	0.093	0.091	0.101	1803	1914	1773	—	—	—
H. B	0.338	0.350	0.346	0.215	0.246	0.232	0.093	0.101	0.104	2290	2090	2305	222	228	198
B. H	0.386	0.376	0.392	0.277	0.254	0.280	0.141	0.123	0.11	1902	1707	1646	67	150	108
F. B	0.252	0.295	0.290	0.173	0.168	0.266	0.109	0.127	0.1 4	4744	4728	4072	—	—	—
W. W	0.376	0.380	0.351	0.258	0.250	0.233	0.118	0.130	0.130	1412	1553	1963	131	162	104
Mean	0.339	0.348	0.36	0.219	0.240	0.214	0.109	0.119	0.122	2279	2260	2203	117	148	122
Standard deviation	0.037	0.029	0.032	0.033	0.030	0.036	0.014	0.017	0.016	1041	1017	860	64	96	44
P value versus control		—	—	—	—	—	—	<0.001	<0.001	—	—	—	—	—	—
P value versus 150		—	—	—	—	—	—	—	—	—	—	—	—	—	—

Abbreviations c = control 150 = after 150 µg clonidine; 300 = after 300 µg clonidine; Q–S₂ = interval bet een Q and aortic second (dynes sec./cm.⁻⁵); PAR = pulmonary arteriolar resist nce (dynes/sec./cm.⁻⁵); LVMWI = left ventricular minut ork index (kilogram- power index (gram meters pe squa meter per second) MRLVEI = mea rat of left entricular ejection index (milliliters per square

persisted for 2 to 6 hours following the study. Supine cuff blood pressure remained below control levels for 3 to 10 hours after the study.

Discussion

A fairly uniform hemodynamic response to clonidine was observed in this group of hypertensive patients. Clonidine 150 µg given intravenously over two and a half minutes produced a modest brief vasopressor response in 5 of the 8 patients. Rapid intravenous injection of this drug can produce acute elevation of blood pressure which might be deleterious. However in our studies the pressor response was brief, not lasting over two and a half minutes, and was not seen in several other studies when the infusion period was increased to 5 minutes. Nayler and associates[1] have shown that the pressor effect is caused by direct peripheral vasoconstriction through alpha receptor stimulation. This can be abolished by phentolamine. Her studies also have demonstrated that it is not due to release of endogenous catecholamines as occurs with some sympathetic blocking agents such as guanethidine and bretylium.

A vasodepressor response was then observed in all 8 patients. The maximum effect occurred within 10 to 20 min. The rapidity with which the agent lowers blood pressure warrants further evaluation in clinical situations which require immediate reduction in blood pressure.

Clonidine 150 µg lowered mean arterial pressure 17 per cent and 300 µg lowered mean arterial pressure 27 per cent. Magnitude of blood pressure fall was grossly related to the control level. Significant hypotension was not produced in any patient with this dose.

The acute reduction of blood pressure was associated with decrease in cardiac output. However, total systemic resistance did not increase as one would predict if the fall in blood pressure were mediated only by a decrease in cardiac output. Instead systemic resistance was unchanged. These findings are in agreement with those of Barnett and Cantor,[13] Onesti and coworkers,[14] and Muir and associates.[11] Normally, if the arterial bed is subjected to lowered flow the bed constricts and calculated resistance rises. Therefore the failure of total systemic resistance to rise in the face of lowered flow reflects ion of

	LVMWI			*LVSWI*			*LVSPI*			*MRLVEI*			*TTI*	
	150	*300*		*150*	*300*		*150*	*300*		*150*	*300*		*150*	*300*
8.1	5.2	3.8	80	55	42	324	210	163	131	107	97	4957	3758	2908
7.7	6.2	4.4	114	75	56	419	318	290	150	155	133	3202	3062	2570
4.4	3.1	2.3	51	44	63	205	177	227	124	133	105	—	—	—
4.9	3.2	4.3	61	44	67	244	173	241	140	119	133	2590	2161	2945
8.9	3.7	3.4	69	42	41	252	171	163	131	89	95	3645	3137	2537
4.3	2.9	1.9	75	44	38	276	173	136	164	130	129	2053	1619	1121
3.3	3.7	2.6	57	40	29	227	236	174	121	107	102	3459	2503	1783
5.7	4.6	3.9	60	45	50	267	220	165	140	125	134	3070	2673	2176
5.5	4.1	3.3	73	50	47	290	209	193	140	130	116	3333	2703	2254
1.4	1.3	0.9	20	12	12	65	50	40	19	21	19	525	700	631
—	<0.001	<0.001	—	<0.001	<0.02	—	<0.001	<0.01	—	<0.01	<0.01	—	<0.01	<0.01
—	—	<0.05	—	—	—	—	—	—	—	—	—	—	—	<0.05

...(seconds) LVET = left ventricular ejection time (seconds) PEP = pre-ejection period (seconds) TSR = total systemic resistance ... meters per square meter) LVSWI = left ventricular stroke work index (gram-meters per square meter); LVSPI = left ventricular stroke ... per second) TTI = tension time index (millimeters [illegible], seconds per minute).

the normal constrictor response of the resistance vessels. Onesti and co-workers did observe a lowering of total systemic vascular resistance in the erect posture after oral administration of clonidine although Barnett and Cantor observed no change in total systemic vascular resistance in the erect position

Changes in the pulmonary circulation were similar to those in the systemic circulation.

After 150 μg clonidine lowering of cardiac output was mediated by decrease in stroke volume after a total dose of 300 μg slowing of heart rate also contributed to the lowering cardiac output.

We believe that the reduction in rate of oxygen consumption is related to the sedation produced by this drug Depression of aerobic metabolism alone does not appear to be of sufficient magnitude to account for the decrease in cardiac output observed in our study

Lowered flow and arterial pressure contributed about equally to the reduction of left ventricula minute work and stroke work.

Clonidine also produced qualitative changes in left ventricular function all of which suggest a lower level of ventricular performance. Stroke power index and mean rate of left ventricular ejection index were decreased and pre-ejection period a reflection of the rate of left ventricular pressure rise during isovolumic contraction [11] was prolonged

The fall in stroke power index is largely related to the lowering of arterial pressure. This fall in blood pressure could not account for the prolongation of pre-ejection period which might be expected to shorten with decreasing arterial pressure. The prolongation of the pre-ejection period may be due to lowered left ventricular filling pressure or due to direct or reflex depression of the myocardium

The mechanism by which clonidine exerted the effects we observed is not elucidated by our study The inhibition of sympathetic centers in the brainstem demonstrated in animal studies results in decreased sympathetic transmission to the heart and vascular bed [4] This finding and the sedation produced by the drug are responsible for the bradycardic effect observed by many investigators.

Studies using isolated human and dog papillary muscle...

but nonsignificant changes in tension developed over a wide dose range of clonidine[17] In dogs with venous return held constant the ability to perform work at the upper end of the left ventricular work curve was slightly reduced[5] Clonidine may have a small but probably insignificant depressor effect on ventricular performance independent of changes in venous return

In our study left ventricular filling pressure as reflected by mean pulmonary artery wedge pressure was decreased This may account for the reduction of stroke volume Changes in mean right atrial pressure were not significant

Ehringer[2] noted an increase in the venous capacity of the leg after clonidine and Nayler and associates[5] noted decreased venous return in animals. Muir and coworkers[14] found central blood volume reduced after clonidine. This redistribution of blood volume is thought to arise through central inhibition of sympathetic transmission to the venous capacitance bed[5] Despite the lack of significant change in right atrial pressure our findings are most consistent with this mechanism of reduction of cardiac output and left ventricular performance

Another possibility is that reduction of left ventricular filling pressure may be secondary to decrease in arterial pressure Acute moderate elevation of arterial pressure results in elevation of left ventricular end diastolic pressure and in the absence of ventricular disease stroke volume usually rises.[8] In our study we may be observing the reverse associated with an acute reduction of arterial pressure.

Summary

Intravenous infusion of 150 μg of clonidine produced a prompt reduction of arterial pressure in a group of 8 patients with arterial hypertension Systolic pressure fell 19 per cent diastolic 16 per cent and mean pressure 17 per cent. A second dose of 150 μg of clonidine given 30 min. later produced further significant change of only systolic pressure which was reduced 28 per cent below control

Changes in the pulmonary circulation were similar in the systemic circulation

Clonidine appears to lower blood pressure through reduction in cardiac output and perhaps by some decrease in tone of resistance vessels. The fall in cardiac output is probably caused chiefly by reduction of left ventricular filling pressure. Central inhibition of sympathetic transmission to the venous capacitance vessels may result in pooling of blood peripherally with lowering of the venous return and cardiac output

REFERENCES

1 Hoefke W and Kobinger W: Pharmakologische Wirkungen des (2 6-Dichlorphenylamino)-2 imidazolin-hydrochlorids, einer neuen antihypertensiven Substanz Arzneimittelforschung 16:1038 1966.
2 Ehringer H Die Wirkung von 2 (2 6, Dichlorophenylamino) 2-imidazolin-hydrochlorid auf die Extremitatendurchblutung den Blutdruck und die venenkapazitat bei Normotonikern, Arzneimittelforschung 16:1165 1966.
3 Kobinger W and Walland A. Kreislaufuntersuchungen mit 2 (2 6-Dichlorophenylamino)-2 imidazolin-hydrochloride Arzneimittelforschung 1 :292 1967
4 Bousquet J R. Guidicelli J F Fichelle, J Schmitt H and Schmitt Mme. H Cardiovascular effect of 2 (2,6-dichlorophenylamino)-2 imidazoline hydrochloride (ST 155) Europ. J Pharmacol 2:333 1968.
5 Nayler W G Price, J M Swann, J B McInnes, I Race, D and Lowe T E. Effect of hypotensive drug ST 155 (Catapres) on the heart and peripheral circulation, J Pharmacol Exp. Ther 161:45 1968.
6 Kobinger W and Wallond A. Investigations into the mechanisms of the hypotensive effect of 2 (2 6-dichlorophenylamino)-2 imidazoline hydrochloride, Europ. J Pharmacol. 2:155 1967
7 Schmitt, H Schmitt, Mme. H Bousquet J R., and Guidicelli, J R Centrally mediated decrease in sympathetic tone induced by 2 (2,6 dichlorophenylamino)-imidazoline hydrochloride (ST 155 Catapresan) Europ. J Pharmacol 2 147 1968.
8. Schmitt, H Schmitt, Mme. H Bousquet J R. Guidicelli J F and Fichelle J Cardiovascular effects of 2 (2 6 dichlorophenylamino)-imidazoline hydrochloride (ST 155) Europ. J Pharmacol. 2:340 1968.
9 Constantine Jay W and McShane, Wilfred K. Analysis of the cardiovascular effects of 2 (2,6-dichlorophenylamino)-2-imidazoline hydrochloride (Catapres) Europ. J Pharmacol. 4 109 1968.
10 Merguet P Heimsoth V Murata T and Bock, K. D Experimental study on the circulatory effects of 2 (2 6-dichlorophenylamino)-2 imidazoline hydrochloride in man, Pharmacol. Clin. 1:30, 1968.
11. Nayler Winifred G., Rosenbaum M., McInnes, I., and Lowe, T E.: Effect of a new h tensive

drug, ST 155 on the systemic circulation, Amer. Heart J 72 764, 1966.

12. Barnett, A. J and Cantor S.. Observations on the hypotensive action of "Catapres (ST 155) in man, Med. J Aust. 1:87 1968.

13. Onesti, G., Schwartz, A. B Kim, K. E., Swartz, C., and Brest, A. B Pharmacodynamic effects of new antihypertensive drug, Catapres (ST 155), Circulation 39:219 1969

14. Muir A. L., Burton, J L., and Lawrie, D. M Circulatory effects at rest and exercise of clonidine, and imidazoline derivative with hypotensive properties, Lancet 2 181 1969

15. Weissler A. M., Harris, W S., and Schoenfeld, C. D : Bedside techniques for the evaluation of ventricular function in man, Amer J Cardiol. 23:577 1969

16. Shaver J A., Kroetz, F W., Leonard, J J and Paley H. W.. The effect of steady-state increase in systemic arterial pressure on the duration of left ventricular ejection time, J Clin. Invest. 47:217 1968.

17 Nayler W G., Price, J M Stone, J and Lowe, T E. Further observations on the cardiovascular effects of ST 155 (Catapres), J Pharmacol. Exp. Ther 166:364 1969

18. Ross, J J and Braunwald, E. The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin, Circulation 29 739 1964.

Observations on murmurs originating from incompetent heterograft mitral valves

Ellen Killebrew, M.D.
Keith Cohn, M.D.
San Francisco, Calif.

Heterograft mitral valves* have recently been found to degenerate after a period of time allowing severe regurgitation to develop; consequently, their use has been abandoned. A series of interesting auscultatory phenomena was detected as these valves became incompetent. Hence, although they ultimately were proved to be unsatisfactory from a therapeutic point of view, the information gleaned regarding sound and murmur generation appears instructive and worthy of discussion. We would like to address ourselves here to three aspects of these murmurs: their occasional musical quality, their radiation, and the rare occurrence of a staccato series of sounds forming a murmur-equivalent.

Musical murmurs

Most cardiac murmurs are composed of random noise; musical murmurs, on the other hand, consist of harmonics of dominant frequency patterns.[1] Musical murmurs have been noted in normal children. Being termed Still's murmurs and often simulating a sea gull's cry, they are seldom if ever indicative of heart disease in this setting.[2] In valvular aortic stenosis, the main portion of the murmur, located at the base of the heart, is typically harsh and nonmusical; this murmur, however, often radiates to the apex with musical overtones—the Gallavardin phenomenon.[3] This auditory effect has been explained by the attenuation of lower frequencies upstream from an impediment to flow; the higher pitched harmonics then become more evident.[3,4] The other commonly recognized musical murmur is the "whoop" or "honk," so named because of its resemblance to a goose call.[4,5] These bizarre murmurs were initially thought to be due to stretching of moderator bands extending across the ventricular chamber or, alternatively, were believed to be extracardiac (pleuropericardial) in origin.[2] More recently, several investigators have associated these unusual bruits with a ballooning of one or both leaflets of the mitral valve, and mitral insufficiency has at times also been found in such cases.[6,7] Nonmusical late systolic murmurs, midsystolic clicks, and abnormal electrocardiograms have also been found in association with honks. Although mitral insufficiency secondary to ruptured chordae

From the Cardiopulmonary Unit and the Institute of Medical Sciences, Pacific Medical Center, San Francisco, Calif.
Supported by Grants HE 05498 and HE 06311, National Institutes of Health, United States Public Health Service, and a grant from the Bay Area Heart Association.
Received for publication June 19, 1970.
Reprint requests to: Keith Cohn, M.D., Cardiopulmonary Unit, Institute of Medical Sciences, Pacific Medical Center, San Francisco, Calif. 94115.
*These valves are semilunar aortic valves from calves or pigs and are mounted on a Teflon-covered metal ring which supports the leaflets and which is sutured onto the mitral annulus.

April 1971, Vol. 81, No. 4, pp. 490-493

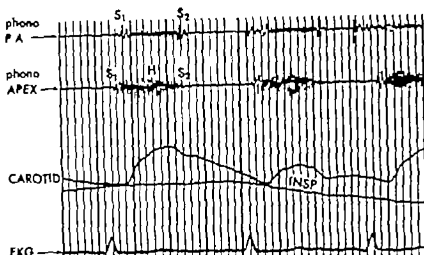


Fig. 1 Systolic apical honk (*H*) recorded from Patient D. L. S_1 and S_2 are the first and second heart sounds, respectively.

tendineae was formerly thought to produce musical murmurs, more recent findings suggest that this is seldom the case.

Initially we would like to discuss the honking musical murmurs heard in three of our patients with mitral heterograft valve insufficiency. These murmurs, considered to be mooing by some of our group since the heterograft was from a calf (or oinking in the case of a porcine heterograft) were found at surgery to be associated with prolapsing leaflets. It seems reasonable to postulate that ballooning prolapsing leaflets become stretched and vibrate in such a fashion as to produce harmonics.

Case history D. L., 53-year-old Caucasian woman with rheumatic mitral stenosis and aortic insufficiency underwent mitral valve replacement with porcine heterograft in May 1968. The patient did well until November 1968 when she developed increasing symptoms of congestive failure. On physical examination, Grade 5/6 honking pansystolic murmur was well heard at the apex with radiation to the axilla, back, right and left sternal borders, and base (Fig. 1). In December 1968, the heterograft was removed and replaced with No. 3 Starr-Edwards prosthesis. At operation, the annulus of the heterograft was noted to be well seated; however doming and prolapse of the graft leaflets were observed.

Machine gun murmur

Another leaking mitral heterograft valve produced an even more unusual type of murmur.

Case history A. C., 59-year-old man, developed mitral regurgitation following an inferior myocardial infarction in 1962. In 1966 he developed subacute bacterial endocarditis with progressive symptoms of congestive heart failure and a loud pansystolic, apical murmur indicative of mitral insufficiency. In March, 1969 the mitral valve was replaced with a porcine heterograft, the previous mitral incompetence being found to be secondary to stretched chordae tendineae and papillary muscle dysfunction. One month later *Serratia marcescens* endocarditis was diagnosed, and was thereafter proved to be refractory to cephalosporin and kanamycin therapy. On April 10, 1969 a machine gun staccato systolic murmur was heard over the entire precordium. The murmur consisted of bursts of sounds in a rapid "rat-a-tat-tat" fashion (Fig. 2). The following day the murmur became more typically pansystolic and the heterograft was replaced with a ball-valve prosthesis. At surgery a large hole was noted in one of the heterograft cusps and thrombus was noted around the valve annulus, mainly at the posterior edge.

Comment This patient had a perforation of one of the valve leaflets and it is likely that the valve flapped as a luffing sail does. This might develop as Rushmer and Morgan have suggested secondary to eddy current formation. Liquids flowing at high velocity through a narrow orifice into a wide channel emerge as rapidly moving multiple jets and eddies form at the interface with the surrounding slow moving liquid. Rodbard and Williams have shown that when the flow rate through a small orifice is high the phenomenon of flitter occurs and the pressure action

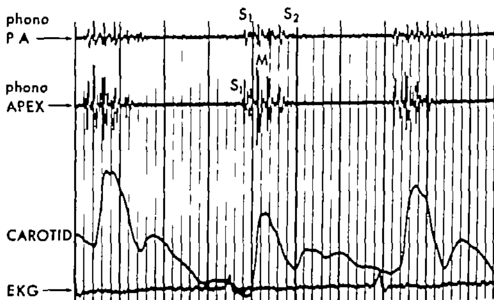


Fig 2 Machine gun murmur (*M*) in Patient A C. Note the staccato series of sounds throughout syst

or atrial wall rises and falls in an oscillatory fashion Hence there are a number of possible mechanisms for production of this unusual murmur The repetitive pressure changes due to flutter or eddy formation might set the mitral valve apparatus into motion thereby producing the staccato series of sounds noted abrupt acceleration or deceleration of a valve cusp could generate such sounds Alternatively the waxing and waning of pressure might play against another resonant structure in the heart causing it to produce the series of discontinuous sounds

Murmur radiation

Case history J C., a 69-year-old man developed severe mitral insufficiency in 1968 due to subacute bacterial endocarditis and rupture of the chordae tendineae. Progressively severe congestive failure evolved over the next several months and in July 1968 he underwent a mitral porcine heterograft replacement of his incompetent valve. He was initially improved but was readmitted to the hospital 5 months later with acute pulmonary edema. On physical examination he was found to have a Grade 4/6 harsh systolic murmur with impressive radiation to the right axilla and right sternal border Cardiac catheterization revealed gross mitral regurgitation, and on Dec. 20 1968 he underwent a ball-valve prosthetic replacement of the heterograft At surgery one entire medial commissure was found to have torn loose.

Radiation of murmurs may be explained simply on the basis of their extreme loudness in some instances or may be accounted for by the direction of blood flow A jet of blood striking a wall might create a radiated murmur much as the ocean wa creates sound as it crashes upon the bea or sea wall In typical rheumatic mit insufficiency radiation of the murmur the back and left axilla has been explain by the regurgitation of blood in a leftwa direction into an enlarged left atrium latter expanding posteriorly as well a transmitting sounds through the verteb osseous structures into the back[3] In ru tured chordae tendineae with poster leaflet prolapse the jet is directed upwa against the atrial septum and the murm is noted to radiate well toward the ba of the heart and even into the neck[10]

Comment In this case the murmur ra ated across the right hemithorax and in the right axilla in our experience and another's experience[4] prominent radiat to this area is quite rare Since the med cusp was one of those which was incomp tent, it seems reasonable to postulate th at least some of the blood was directed in jetlike fashion toward the right lung

Summary

Three cases of mitral valve heterogra incompetence are reported each demo strating an instructive principle regardi the genesis of murmurs. One patient had musical honking systolic murmur relat to leaflet doming and prolapse A seco patient had a machine gun murmur staccato series of sounds most likely p duced by pressure oscillations broug

about by a perforation in one of the cusps. The third patient had an unusual radiation of his murmur to the right hemithorax and axilla, this being due it is believed to an unusually directed regurgitant jet.

REFERENCES

1. Rushmer R., and Morgan, C. Meaning of murmurs, Amer J Cardiol 21 722 1968.
2. McKusick, V Murmurs, cardiovascular sound in health and disease, Baltimore, 1958, The Williams & Wilkins Company
3. Rodbard, F Symposium on cardiovascular sound, Circulation 16:270, 1957
4. Feinstein, A. Acoustic distinctions in cardiac auscultation, Arch. Intern. Med. 121:209 1968.
5. Behar V S. Whalen, R. E and M I tosh, H. D.: The ballooning mitral valve in patients with the precordial honk or whoop, Amer J Cardiol. 20 789 1967
6. Rackley C. E., Whalen, R. E., Floyd W L., et al. The precordial honk, Amer J Cardiol. 17:509 1966.
7. Bittar N and Sosa, J : The billowing mitral valve leaflet, Circulation 38:763 1968
8. Barlow J B and Bosman, C. K.: Aneurysmal protrusion of the posterior leaflet of the mitral valve, AMER. HEART J 71 166, 1966.
9. Leon, D F Leonard, J J Kroetz, F W et al.: Late systolic murmurs, clicks and whoops arising from the mitral valve, AMER. HEART J 72:325 1966.
10. Selzer A. Kelly J J Vannitamby M et al. The syndrome of mitral insufficiency due to isolated rupture of the chordae tendineae Amer J Med. 43:822, 1967

Left atrial pressure during exercise in hemodynamic normals

Russell V. Luepker, M.D.
Stig Holmberg, M.D.
Edvardas Varnauskas, M.D.
Gothenberg, Sweden

Reported changes in mean left atrial pressure in exercising subjects have varied. Increases, decreases, and unaltered pressures from resting levels with direct or pulmonary wedge methods have been observed.[1-4] During the study of individuals without demonstrable cardiopulmonary disease, a consistent pattern was noted during supine submaximal exercise in this laboratory. A rapid increase in mean left atrial pressure to a maximum at the second to fourth minutes of exercise was followed by a slower decline to levels near or below those of rest conditions. Similar patterns for the pulmonary artery and aortic pressure response to exercise have been described by other investigators.[5-9]

Cognizance of this time related pressure phenomenon may be useful in the understanding of left heart and pulmonary circulatory responses to exercise and also in the definition of human exercise "steady state."

Methods

Seven individuals, three female and four male, ranging in age from 27 to 50 are included in this study (Table I). Investigations were performed to evaluate cardiac murmurs and/or atypical chest pain. In those with chest pain, coronary arteriograms and coronary blood flow measurements were performed.[10] No evidence of cardiovascular disease by catheterization, radiographic, or other clinical and laboratory methods was demonstrable except in one subject who was mildly hypertensive. All individuals were judged hemodynamically normal.

Investigations were performed in the morning on the fasting, unpremedicated subjects. In the supine position, transseptal and other catheters were positioned as described elsewhere.[11] Local anesthetic for catheter insertion and small amounts of heparinized saline to prevent catheter clotting were the only medications employed.

Pressure gauges (EMT 490A or Statham P23 Db) were positioned 5 cm. below the sternal angle. Zero and standard levels were taken before and after each set of pressure measurements. The pressure tracings were recorded photographically and electronically integrated. Dynamic characteristics of the catheter manometer system was tested in a few instances. These were linear to 5 to 10 c.p.s. However, because of the response variability, dynamic pressure data is not included in this presentation.

From the First Medical Clinic, University of Gothenberg, Gothenberg, Sweden.
Supported in part by a grant from the Swedish National Foundation against Heart and Lung Diseases.
Received for publication June 29, 1970.
Reprint requests to: Stig Holmberg, M.D., Medical Clinic I, Sahlgren Hospital, Gothenberg, Sweden.

April 1971 Vol. 81 No. 4 pp. 494-497

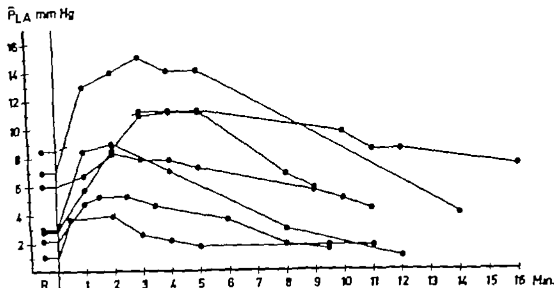


Fig. 1 Mean left atrial pressure (MLAP) compared with time in exercising subjects.

The subjects feet were placed in a variable load electronically braked bicycle ergometer. This device maintains a constant load regardless of pedalling rate within a range of 45 to 75 r.p.m.[8] The bicycle pedals had an axis 10 cm above the fluoroscope bed. Control readings were taken after a minimum of 5 minutes rest after the feet were placed on the ergometer pedals. Following control the subject began exercise at a load (100 to 400 kpm per minute predetermined by tests of exercise capacity. All subjects maintained continuous exercise without chest pain or other difficulty for ten or more minutes.

Pressure measurements are the average of three or more respiratory cycles.

Results

Fig. 1 presents the change in mean left atrial pressure with time for each subject. The average left atrial pressure at rest was 4.8 mm. Hg which is comparable to results from similar subject groups by other authors.

In Fig. 2 the average pressure changes with time are shown. A maximum of 8.6 mm. Hg is reached during the third minute of exercise and values decline progressively until at ten minutes exercise when it is lower than the rest pressure.

Fig. 3 shows typical pressure wave configurations from the left atrium at rest and during exercise. It is apparent that the wave form is unchanged but displaced upward with exercise. The relative contribution of the "a" and the "v" waves to mean left atrial pressure varies little with exercise.

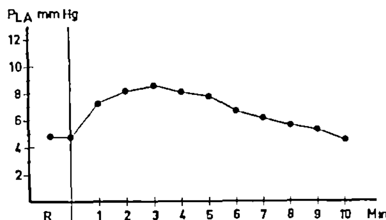
There was no demonstrable relationship of the mean left atrial pressure data to age or sex in this small group.

Table I

Subjects				
N	Initial	Age	Sex	Clinical problem
1	UW	30	F	Functional murmur
2	EB	47	F	Normal-poor conditioning
3	EO	50	F	Atypical chest pain
4	VK	41	M	Atypical chest pain BP 160/90
5	BE	46	M	Atypical chest pain
6	OI	27	M	Functional murmur
7	PG	45	M	Atypical chest pain

Discussion

Reports of the mean left atrial pressure response (MLAP) to supine submaximal exercise in subjects have varied.[4] The



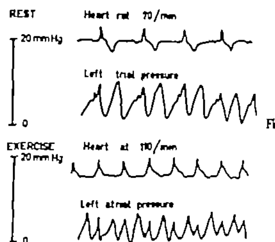


Fig 2 Average left atrial pressure compared with time during exercise
Fig 3 Comparison of the rest with the exercise left atrial pressure configuration in one subject (UW)

time related pressure phenomenon described here may account for this observed variability Depending on the instant of measurement one can confirm increases decreases or unchanged pressure responses to exercise

Earlier exercise studies of pulmonary artery pressure demonstrated time related patterns similar in magnitude and configuration to those described here for the mean left atrial pressure[8,9] It was proposed by Slonim and associates[8] that pressure changes in the left heart might account for this observation but this factor was not directly measured The present data support this proposition

The origin and significance of this pattern in left atrial pressure can only be speculated from this study The left atrium as a dynamic filling chamber for the left ventricle is strongly affected by the diastolic phase in that chamber Left ventricular end diastolic pressure has been observed to parallel mean left atrial pressure in normal individuals at rest and during stress[2,17] A biphasic left ventricular diastolic pressure response to exercise has been documented in animals by Guyton and co-workers[18] With exercise there is an initial (within seconds) increase in venous inflow and increased ventricular filling pressures This response is believed to represent a Starling mechanism of increased contractility with a pressure volume load After a minute however sympathetic tone becomes an increasing factor and the ventricle shifts its Starling curve to yield the increased output at lower filling pressures. Left ventricular diastolic pressure then declines. This biphasic response to work could explain the initial increase and subsequent slow decline in mean left atrial pressure observed here

Other factors known to operate during exercise should also be considered Intrapleural pressure declines with exercise and increased negative pressure affects intrathoracic structures. This would tend to lower not raise measured intracardiac pressures with exertion[9]

Aortic or systemic pressures show a slow decline with sustained exercise Thus the pressure demand on the left heart with time becomes lower This also may be a factor

Multiple conditions are known to affect hemodynamic parameters in exercising subjects. Position mode repetition and duration of exercise are among those demonstrated to affect hemodynamics The existence of this time related pressure phenomenon is another factor which should be considered when exercise-evoked phenomenon related to left atrial pressure are examined under conditions similar to those described in this study

Summary

Mean left atrial pressure during supine submaximal exercise was studied in seven hemodynamic normal individuals. A rapid increase in pressure to a maximum at the second to fourth minute of exercise followed by a slow decline to levels near or below those of rest conditions was noted in

all individuals. A possible mechanism relating left ventricular exercise response to left atrial pressure is discussed

REFERENCES

1 Dexter L., Wittenberger J Haynes, F Goodale, W Gorlin, R., and Sawyer C. Effect of exercise on circulatory dynamics of normal individuals, J Appl. Physiol. 3:439 1951
2. Kasalicky J Hurych, J Widimsky J Dejdar R., Metys, R., and Stanek, V Left heart haemodynamics at rest and during exercise in patients with mitral stenosis, Brit. Heart J 30 188, 1967
3. Yu, P Murphy G., Schreiner B., and James, D Distensibility characteristics of the human pulmonary vascular bed, Circulation 35 710 1967
4 Ekelund, L and Holmgren, A. Central hemodynamics during exercise, Circulation 20 (Suppl. 1) 1 1967
5. Holmgren, A Jonsson, B., and Sjostrand, T Circulatory data in normal subjects at rest and during exercise in the recumbent position, Acta Physiol. Scand. 49:343 1960.
6. Slonim, N Ravin, A., Balchum, O and Dressler S. The effect of mild exercise in the supine position on the pulmonary arterial pressure of five normal human subjects, J Clin. Invest. 30 1022, 1951.
7 Barratt-Boyes, G. and Wood, E. Hemodynamic response of healthy subject to exercise in the supine position while breathing oxygen, J Appl. Physiol 11 129 1957
8. Sancetta, S and Rakita, L. Response of pulmonary artery pressure and total pulmonary resistance of untrained, convalescent man to prolonged mild steady state exercise, J Clin. Invest. 36 1138, 1957
9 Widimsky J Bergland, E., and Malmberg, R. Effect of repeated exercise on the lesser circulation, J Appl. Physiol. 18:983, 1963
10. Holmberg, S Paulin, S., Prerovsky I and Varnauskas, E.: Coronary blood flow in man and its relation to the coronary arteriogram Amer J Cardiol. 19:486 1967
11. Varnauskas, E., Forsberg, S., Widimsky J and Paulin, S. Pulmonary blood volume and its relation to pulmonary hemodynamics in cardiac patients, Acta Med. Scand. 173:529 1963.
12. Holmgren, A., and Mattsson, K. H A new ergometer with constant work load at varying pedal rate, Scand. J Clin. Lab. Invest. 6 137 1954.
13. Mitchell, J Gilmore, J and Sarnoff S. The transport function of the atrium, Amer J Cardiol. 9:237 1962.
14. Braunwald, E., and Frahm, C.: Studies on Starling law of the heart. IV Observations on hemodynamic functions of the left atrium in man, Circulation 24:633, 1961
15 West, J Dollery C., and Naimark, A. Distribution of blood flow in isolated lung in relation to vascular and alveolar pressures, J Appl. Physiol. 19 13, 1964
16. Karp R., Graf P and Nadel, J. Regulation of pulmonary capillary blood volume by pulmonary arterial and left atrial pressures, Circ. Res. 22 1 1968.
17 Ross, J Gault, J Mason, D Linhart, J and Braunwald, E. Left ventricular performance during vascular exercise in patients with and without cardiac dysfunction, Circulation 34:597 1966.
18 Guyton, A., Douglas, B., Langston, J and Richardson, T.: Instantaneous increase in mean circulatory pressure and cardiac output at onset of muscular activity Circ. Res. 11:431 1962.

Right precordial qrS pattern due to left anterior hemiblock

Paul L. McHenry, M.D.
John F. Phillips, M.D.
Charles Fisch, M.D.
*Betty R. Corya, M.D.**
Indianapolis, Ind.

Myers and his associates were the first to correlate the electrocardiographic pattern of a small q, small r, large S (qrS) in the right precordial leads with histological evidence of septal myocardial infarction.[1,2] The finding of a qrS pattern in V_2 or V_1 and V_2 is generally assumed to be indicative of a septal myocardial infarction. Recently Rosenbaum and associates described the appearance of an identical qrS pattern in V_2 in patients with abnormal left axis deviation thought to be due to conduction block in the anterior division of the left bundle branch system (anterior hemiblock).[3,4] They suggested that the initial q wave in V_2 with anterior hemiblock may be the result of inferior and posterior deviation of the initial septal vector. If this is indeed so, then right precordial leads obtained at a lower interspace will record the inferiorly oriented initial vector as a positive deflection giving an rS pattern rather than a qrS complex.

The purpose of this communication is to present five patients with a qrS pattern in Lead V_2 accompanying left anterior hemiblock and to suggest that in none of these was the electrocardiogram (ECG) pattern indicative of septal myocardial infarction.

Methods and results

Five patients presenting with left anterior hemiblock and a qrS pattern in V_2 constitute the study group. A detailed medical history was obtained from each patient and his previous medical records were reviewed for evidence of arteriosclerotic heart disease manifest either as angina or myocardial infarction. In each instance a complete physical examination was performed and routine laboratory studies were obtained. A routine ECG and a right precordial ECG mapping was performed on all five patients with Leads V_1, V_2, and V_3 being recorded in the third, fourth, and fifth interspaces.

In none of the patients was there a history of angina or myocardial infarction and none had evidence of overt cardiac disease. In all patients the routine ECG demon-

From the Krannert Institute of Cardiology, Marion County General Hospital, and the Department of Medicine, Indiana University School of Medicine, Indianapolis, Ind.

Supported in part by the Herman C. Krannert Fund, United States Public Health Service Grants HE-4308, HTS-5361, and HE-5749, the Indiana Heart Association, and the American Medical Association Committee for Research on Tobacco and Health.

Received for publication July 7, 1970.

Reprint requests to: Dr. Paul L. McHenry, Department of Medicine, Indiana University Medical Center, 1100 West Michigan St., Indianapolis, Indiana 46202.

*United States Public Health Service Trainee in Cardiology, Department of Medicine, Indiana University School of Medicine.

April 1971, Vol. 81, No. 4, pp. 498-502

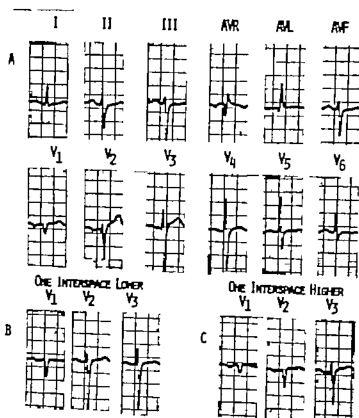


Fig. 1 A, B, and C. 51 year-old man. A. The routine ECG demonstrates an abnormal left axis deviation with a QS in V and qrS in V and V. B. The right precordial q waves are absent in recording taken in the fifth interspace. C. The right precordial q ves are accentuated in recording taken in the third interspace.

strated a qrS complex in V (Figs. 1 to 5 A). However when V was recorded in the fifth interspace the initial q wave was absent (Figs. 1 to 5 B). On the other hand when the right precordial leads were recorded in the third interspace the initial q wave in V became more prominent and in some cases a small initial q wave became apparent in V or V (Figs. 1 to 5 C).

Discussion

The original studies of Myers correlating the qrS pattern in V or V and V with septal myocardial infarction lack information about the electrical axis of the ECG. More recently Rosenbaum and co-workers stated that an identical qrS pattern can appear in Lead V as a result of a conduction block in the anterior division of the left bundle branch in the absence of myocardial infarction. They suggest that in the normal heart the initial anterior and right ward septal vector is the resultant of early depolarization forces arising from the proximal distributions of the two divisions of the left bundle branch rather than from the main left bundle branch. When the anterior division of the left bundle is blocked the initial septal vector is determined solely by the early forces arising from the inferior division causing it to deviate in an inferiorly and posteriorly direction. This deviation of the septal vector can result in the recording of an initial q wave in Leads V or V and V. If these leads are recorded at a lower precordial position the angle subtended by the lead axis will result in an initial positive vector with an rS pattern recorded in V and V. The present study tends to support these contentions. None of our five patients with left anterior hemiblock and a qrS pattern in V had clinical evidence of myocardial infarction and in every case the qrS pattern was absent in

Right precordial qrS pattern due to left anterior hemiblock

Paul L. McHenry, M.D.
John F. Phillips, M.D.
Charles Fisch, M.D.
*Betty R. Corya, M.D.**
Indianapolis, Ind.

Myers and his associates were the first to correlate the electrocardiographic pattern of a small q, small r, large S (qrS) in the right precordial leads with histological evidence of septal myocardial infarction.[1,2] The finding of a qrS pattern in V_1 or V_1 and V_2 is generally assumed to be indicative of a septal myocardial infarction. Recently Rosenbaum and associates described the appearance of an identical qrS pattern in V_1 in patients with abnormal left axis deviation thought to be due to conduction block in the anterior division of the left bundle branch system (anterior hemiblock).[3,4] They suggested that the initial q wave in V_1 with anterior hemiblock may be the result of inferior and posterior deviation of the initial septal vector. If this is indeed so, then right precordial leads obtained at a lower interspace will record the inferiorly oriented initial vector as a positive deflection giving an rS pattern rather than a qrS complex.

The purpose of this communication is to present five patients with a qrS pattern in Lead V_1 accompanying left anterior hemiblock and to suggest that in none of these was the electrocardiogram (ECG) pattern indicative of septal myocardial infarction.

Methods and results

Five patients presenting with left anterior hemiblock and a qrS pattern in V_1 constitute the study group. A detailed medical history was obtained from each patient and his previous medical records were reviewed for evidence of arteriosclerotic heart disease manifest either as angina or myocardial infarction. In each instance a complete physical examination was performed and routine laboratory studies were obtained. A routine ECG and a right precordial ECG mapping was performed on all five patients with Leads V_1, V_2, and V_3 being recorded in the third, fourth, and fifth interspaces.

In none of the patients was there a history of angina or myocardial infarction and none had evidence of overt cardiac disease. In all patients the routine ECG demon

From the Krannert Institute of Cardiology, Marion County General Hospital, and the Department of Medicine, Indiana University School of Medicine, Indianapolis, Ind.

Supported in part by the Herman C. Krannert Fund, United States Public Health Service Grants HE-6304, HTS-5363, and HE-5749, the Indiana Heart Association, and the American Medical Association Committee for Research on Tobacco and Health.

Received for publication July 7, 1970.

Reprint requests to: Dr. Paul L. McHenry, Department of Medicine, Indiana University Medical Center, 1100 West Michigan St., Indianapolis, Indiana 46202.

*United States Public Health Service Trainee in Cardiology, Department of Medicine, Indiana University School of Medicine.

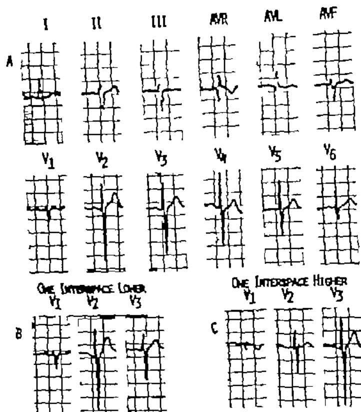


Fig. 3 *A*, *B* and *C*, 33-year-old man. *A*, The routine ECG demonstrates an abnormal left axis deviation with a qrS in V . *B*, The initial q wave is absent when V is recorded i the *fifth* interspace. *C*, I the third inter-space initial q waves are present in V to V

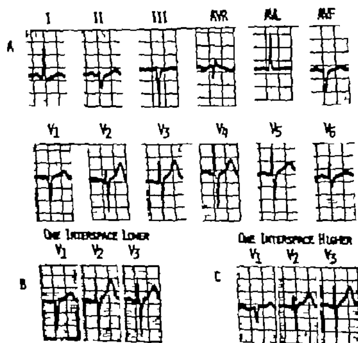


Fig. 4 *A*, *B* and *C*, 56-year-old oman. *A*, The routine ECG demonstrates an abnormal left axis deviation with QS in V and qrS in V . *B*, The initial q wave is absent when V is recorded in the fifth interspace. *C*, There is no change in the initial q wave in V in the third interspace.

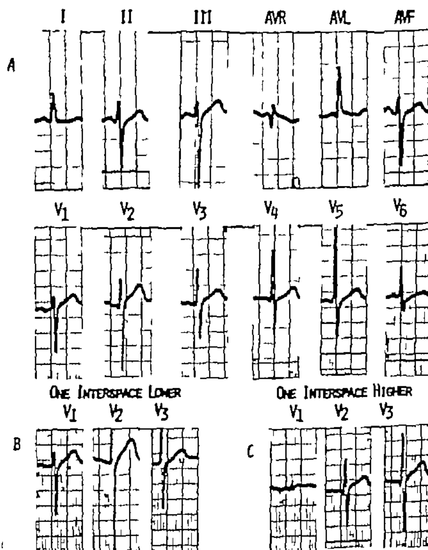


Fig 2 *A* *B* and *C* 57 year-old man *A* The routine ECG demonstrates an abnormal left axis deviation with a qrS in V_2. *B* The initial q wave is absent when V is recorded in the fifth interspace *C* In the third interspace, initial q waves are present in V to V_3.

the ECG recorded one interspace lower than the usual site. Since left anterior hemiblock is frequently indicative of varying degrees of myocardial disease we must assume that all our patients did indeed have myocardial disease However diffuse myocardial fibrosis rather than a well defined myocardial infarction is a more common cause of anterior hemiblock.[6,7] The absence of a history of myocardial infarction in these patients and the consistent appearance of an initial positive vector in recordings obtained in the fifth interspace support the contention that the qrS pattern associated with left anterior hemiblock may be secondary to the intraventricular conduction defect and should not be accepted as unequivocal evidence of myocardial infarction The appearance of a positive initial vector at a lower interspace is likewise against septal fibrosis without conduction block as the cause of the initial right precordial q waves. An incomplete conduction block in the main left bundle may also give initial right to left septal forces but the presence of a q wave in Leads I and/or aVL in all our cases rules against this as the cause of the right precordial qrS pattern

Summary

Five patients with left anterior hemiblock and a qrS pattern in V_2 were studied In each instance the q wave disappeared when V_2 was recorded in the fifth interspace and was accentuated when recorded in the third interspace None of the patients had

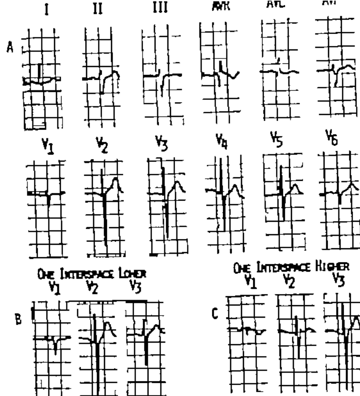


Fig. 3, *A* *B* and *C* 32 year-old man. *A* The routine ECG demonstrates an abnormal left axis deviation with qrS in V *B* The initial q wave is absent when V is recorded in the fifth interspace. *C* I the third interspace, initial q waves are present in V to V.

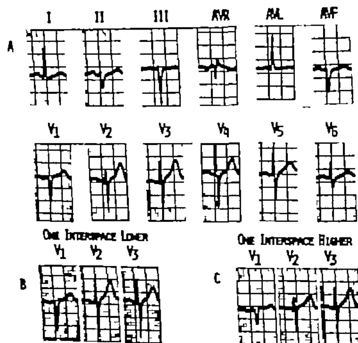


Fig. 4 *A* *B* and *C*. 56-year-old oman *A* The routine ECG demonstrates abnormal left axis deviation ith QS in V and qrS in V *B* The initial q ave is absent when V is recorded in the fifth interspace. *C*, There is no change in the initial q wave in V in the third interspace.

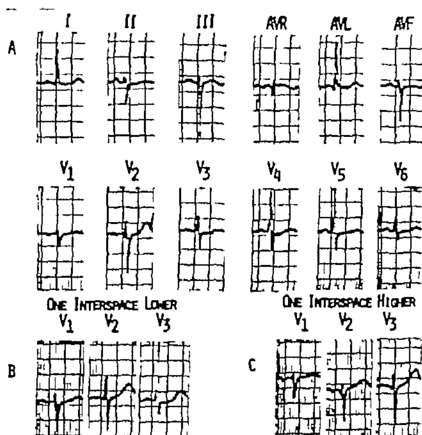


Fig 3 A B and C 42 year-old woman. A The routine ECG demonstrates an abnormal left axis deviation with a qrS in Lead V B The initial q wave is absent when V_2 is recorded in the fifth interspace C, Initial q waves appear in Leads V to V when they are recorded in the third interspace.

a history of myocardial infarction or were suspected of having arteriosclerotic heart disease It is suggested that in the presence of marked left axis deviation q waves in V_2 or V_1 and V_2 may not be due to myocardial infarction

REFERENCES

1 Myers, G. B., Klein, H A and Stofer B E Correlation of electrocardiographic and pathologic findings in anteroseptal infarction Amer. Heart J 36:535 1948.

2. Myers, G B Klein, H A. and Hellerstein T Correlation of electrocardiographic and pathologic findings in infarction of the interventricular septum and right ventricle, Amer. Heart J 37 720 1949

3 Rosenbaum M B, Elizari M V and Lazzari, J O Los hemibloqueos, Buenos Aires, 1967 Ed P Idos.

4 Castellanos, A and Lemberg L Re-evaluation of septal activation in the human heart Amer. Heart J 78:575 1969

5 Pryor R. and Blount S G The clinical significance of true left axis deviation, Amer. Heart J 72:391 1966.

6. Castle, H C. and Keene W M Electrocardiographic peri-infarction block, Circulation 31:403 1965.

Experimental and laboratory reports

Relative effectiveness of three antiarrhythmic agents in the treatment of ventricular arrhythmias in experimental acute myocardial ischemia

Allen B. Weisse, M.D.
Christos B. Meschos, M.D.
Anthony J. Passannante, M.D.
Mohammad I. Khan, M.D.
Timothy J. Regan, M.D.
Newark and Jersey City, N. J.

Although a variety of agents has been found to have some effect on the ventricular arrhythmias that occur during experimental acute myocardial ischemia,[1-4] there has been no comparative study of the drugs which are frequently used clinically to determine their relative advantages. Differences in the response to antiarrhythmic agents have previously been observed during digitalis-induced ventricular tachycardia.

One of the problems with drug evaluation during myocardial infarction is the heterogeneity of treated patients. In addition to age and sex differences, the prior state of the myocardium in terms of scar or hypertrophy or coexistent heart failure or hypotension may be important determinants of the cardiac response as well as the incidence of side effects. The time from the onset of the period of acute myocardial ischemia might also be a crucial determinant of the incidence of ventricular arrhythmias and the responsiveness to the drug.

For this study we employed the intact, anesthetized male dog of relatively young age. Obstruction of a major branch of the left coronary artery near its origin was induced by a gradually occluding thrombus. This resulted in a substantial reduction of blood flow to below 30 ml. per 100 Gm. per minute, associated with S-T-segment elevation and ventricular ectopic beats which untreated progressed to tachycardia and fibrillation.[4] Ischemia produced in this way was unaccompanied by hypotension. Other advantages of this model include the absence of coronary atherosclerosis and previous myocardial infarction and the opportunity for clinicopathologic correlation.

Utilizing this preparation, we have compared the effectiveness of procainamide, lidocaine, and diphenylhydantoin in controlling these arrhythmias following their appearance as well as determining the value of prophylactic administration of the drug following ischemia but preceding the onset of ventricular ectopic beats. The results of this study indicate that in the previously undamaged heart procainamide may be more effective than the other two agents in

From the Department of Medicine, New Jersey College of Medicine and Dentistry, Newark, N. J., and the Thomas J. White Cardiopulmonary Institute, B. S. Pollak Hospital, Jersey City, N. J.
Supported in part by National Institutes of Health Grants 5 R01 FR 05393 and 5 R01 HE 09914.
Received for publication April 6, 1970.
Reprint requests to: Allen B. Weisse, M.D., New Jersey College of Medicine and Dentistry, Department of Medicine, 100 Bergen St., Newark, N. J. 07103.

treating ventricular arrhythmias complicating acute myocardial infarction With none of the drugs did prophylactic administration enhance the ultimate success rate in preventing ventricular fibrillation

Methods

Apparently healthy young male mongrel dogs were anesthetized with morphine sulfate (3 mg per kilogram) and pentobarbital (12 mg per kilogram) placed in the right lateral decubitus position and monitored by electrocardiogram After insertion of an endotracheal tube respiration was assisted by a Harvard pump to assure optimal ventilation [7] No additional morphine was administered during the study period although in some dogs in which spontaneous movement occurred as anesthesia began to wear off an additional dose of pentobarbital (3 to 4 mg per kilogram) was slowly administered intravenously Such supplementary doses of pentobarbital have been shown not to modify hemodynamics in the dog [8] The left jugular vein was isolated and polyethylene tubing advanced through it to the superior vena cava for administration of antiarrhythmic medication Acute coronary occlusion was then induced by a modification of the method of Salazar [9] whereby a thrombus is formed in either main branch of the left coronary artery by a catheter electrode introduced under fluoroscopic guidance via the left common carotid artery For the anterior descending branch the catheter tip is advanced approximately 1 cm beyond its origin and for the circumflex 2 cm beyond its origin A wire is then advanced 2 to 4 mm beyond the tip of the catheter The proximal end of the wire is attached to the positive terminal of a 6 volt dry-cell battery The negative terminal is attached by clamp to the chest wall of the animal The amount of current delivered is regulated by means of a 1 megohm potentiometer 300 to 800 microamperes (μamp) being the range required for thrombosis of blood elements within the arterial lumen

Marked reduction in coronary flow due to thrombus obstruction by this technique results in S-T elevation in appropriate electrocardiographic leads. The time for this to occur usually involves between 30 to 60 minutes for the anterior descending branch and 45 to 90 minutes for the generally larger circumflex branch Angiographically occlusion has been shown to be complete in two thirds of the dogs and over 75 per cent in the remainder [9] Within 5 to 10 minutes following S-T elevation ventricular ectopic beats appear and within 4 hours ventricular tachycardia and fibrillation are observed in approximately 90 per cent of animals in the absence of antiarrhythmic medication [9]

A total of 170 dogs comprise the study group in which the effect of coronary obstruction on cardiac rhythm was observed Twenty dogs in which anterior descending occlusion was accomplished served as a control group to which no treatment was given Additional animals were excluded from the control and treatment groups if catheter occlusion of an artery occurred causing almost immediate S-T elevation or if following thrombus formation ventricular tachycardia appeared within one minute of the injury potential to eliminate the problem of late delivery of the therapeutic agent. In the remaining 150 dogs the effect of procainamide (10 mg per kilogram per dose) lidocaine (3 mg per kilogram per dose) or diphenylhydantoin (5 mg per kilogram per dose) in reversing ventricular arrhythmias (VA) after acute myocardial ischemia was evaluated The drug was administered either following the appearance of 6 or more ventricular ectopic beats per minute after S-T segment elevation ("treatment only" groups) or after sustained S-T elevation (3 to 5 minutes) but preceding the appearance of VA with additional drug administered as necessary following the appearance of VA ("prophylaxis plus treatment") The 150 dogs comprising the 6 therapeutic groups were distinguished as follows

Group IA	Procainamide–treatment only	(39 dogs)
Group IB:	Procainamide–prophylaxis + treatment	(21 dogs)
Group IIA	Lidocaine–treatment only	(29 dogs)
Group IIB	Lidocaine–prophylaxis + treatment	(14 dogs)
Group IIIA	Diphenylhydantoin–treatment only	(27 dogs)
Group IIIB	Diphenylhydantoin–prophylaxis + treatment	(20 dogs)

In both subgroups (A and B) for each drug the initial dose was administered over approximately a one-minute period additional drug in amounts equal to all or half the initial dose were given until cessation of the arrhythmia or death of the animal. Results were grouped under two categories those surviving less than 4 hours following S-T-segment elevation (failure) and those surviving 4 hours or longer (success) following which the animals were put to death with intravenous KCl In either case post mortem examination was performed to confirm the presence of thrombus and its location and the absence of other cardiac abnormalities (heart worms congenital defects, pericarditis etc.)

Evaluation of a selective effect of the artery chosen for occlusion (anterior descending or circumflex) upon success and comparison of the different therapeutic groups was performed by means of the chi-square test. Comparison of the dosages utilized for each drug in the subgrouping for each drug was accomplished by the Student t test.

Results

Controls In all 20 of the untreated control dogs in which anterior descending occlusion was accomplished ventricular premature beats developed following S-T-segment elevation. In 18 dogs this progressed to ventricular fibrillation and death within 4 hours. In the other 2 dogs, although ventricular premature beats occurred they did not progress into fibrillation and the dogs were alive at the time of sacrifice 4 hours later

Therapeutic groups—Effect of artery occluded on preventing ventricular fibrillation. The results of the 6 different therapeutic regimens and their relationship to the artery occluded are indicated in Table I In order to determine the effect, if any of the artery used on the success in preventing ventricular fibrillation the chi-square test was used for each of the 6 groups (i.e. anterior descending versus circumflex for Groups IA, IB IIA, etc.) In all groups except Group IIB (lidocaine prophylaxis plus treatment) where the difference approached significance ($0.1 < p > 0.05$) the differences between the two branches were not statistically significant. The subtotal figures for success and failure with the two branches were also compared and the differences were not found to be significant ($p > 0.05$) These analyses indicated that the arterial branch occluded did not influence the success or failure of therapy and therefore the results from the two arterial occlusion sites were grouped as indicated in the last two columns of Table I in order to compare the different therapeutic groups.

Comparison of therapeutic regimens The results obtained in the 6 therapeutic groups are indicated in Table I with statistical comparisons summarized in Table II Among the "treatment only" groups, procainamide was superior to both lidocaine and d phenylhydantoin there being no significant difference between the latter two (A in Table II) Prophylactic administration of drugs before the onset of ventricular ectopic beats demonstrated no advantages over administration following their onset (B in Table II) All dogs not receiving prophylaxis developed ventricular arrhythmias among the "prophylaxis plus treatment groups these were prevented in only 3 dogs—one instance in each of the 3 prophylaxis groups (IB IIB IIIB) Among the "B" groups procainamide and diphenylhydantoin were equally effective, with a higher survival rate than with lidocaine (C in Table II) but this difference was not significant.

Of the 57 failures that occurred among all 6 groups, 45 occurred within the first hour of S-T-segment elevation

Dosages of drugs administered. The total amounts of drugs used among each of the 6 groups is indicated in Table III Although higher values are indicated in each instance comparing the longer survivors to the failures, the differences are not statistically significant—the minor differences simply reflecting the fact that the longer the survival, the longer the period for ventricular arrhythmias to reappear thus requiring additional drug While not monitored in all animals, in those experiments in which arterial pressure was measured there were variable transient drops in blood pressure after procainamide or diphenylhydantoin which did not seem to interfere with antiarrhythmic action. With the doses used in

Table I. Success of antiarrhythmic agents in preventing ventricular fibrillation following left coronary branch occlusion

Group	No. of dogs					
	Anterior descending branch		Circumflex branch		Totals	
	Failure	Success†	Failure*	Success†	Failure*	Success†
IA Procainamide—treatment only	4	16	4	15	8	31(80)‡
IB Procainamide—prophylaxis plus treatment	2	3	5	11	7	14(67)
IIA Lidocaine—treatment only	6	4	10	9	16	13(45)
IIB Lidocaine—prophylaxis plus treatment	0	3	7	4	7	7(50)
IIIA Diphenylhydantoin—treatment only	3	8	9	7	12	15(56)
IIIB Diphenylhydantoin—prophylaxis plus treatment	2	8	5	5	7	13(65)
Subtotals	17	42	40	51	57	93(62)
Totals	59		91		150	

*Number of dogs surviving less than 4 hours following occlusion.
†Number of dogs surviving 4 or more hours following occlusion.
‡Per cent in parentheses.

this study for all 3 drugs such adverse effects as higher degrees of A-V block or marked widening of the QRS complex were only rarely seen and then it could not be determined if this was due to drug dosage or a direct effect of ischemia on the conduction system.

Discussion

Both procainamide (PA) and lidocaine decrease ventricular excitability and have proved effective in a variety of clinical settings[11-13] although the antiarrhythmic dose of PA is approximately four to five times that of lidocaine[14] and is associated with greater peripheral vasodilating effects.[15] The duration of the antiarrhythmic effects of lidocaine and diphenylhydantoin (DPH) is brief (10 to 20 minutes) whereas considerable amounts of PA are bound to various organs which may serve as reservoirs resulting in a slower decline in plasma levels and more prolonged action.[16] DPH differs from both PA and lidocaine in that it enhances atrioventricular conduction[4] while the other two agents have variable effects.[17]

The apparent superiority of PA in the present study is probably not related to insufficient dosages of the other agents. Although theoretically the more rapid decline in plasma levels of lidocaine and DPH as compared to PA may have made arrhythmia control more difficult with these agents, rapid administration was accomplished by means of a drug filled syringe always at readiness attached to a central venous catheter during constant electrocardiographic monitoring. Termination of the arrhythmia rather than any predetermined amount of drug was the end point for dosage. The fact that dosages administered to the successes and failures of each of the groups were comparable further supports the contention that inadequate dosage was not a factor effecting results in this study. Nor by the same reasoning can the failures be attributed to excessive dosage

Table II. Statistical evaluation of various drug regimens in preventing ventricular fibrillation

Therapeutic groups	P value	Comment
A. Treatment only		
IA vs. IIA (P vs. L)	<0.005	P superior
IA vs. IIIA (P vs. D)	<0.05	P superior
IIA vs. IIIA (L vs. D)	>0.25	NS
B. Treatment only vs. prophylaxis plus treatment		
IA vs. IB (P)	=0.25	NS
IIA vs. IIB (L)	=0.75	NS
IIIA vs. IIIB (D)	>0.40	NS
C. Prophylaxis plus treatment		
IB vs. IIB (P vs. L)	>0.25	NS
IB vs. IIIB (P vs. D)	>0.70	NS
IIB vs. IIIB (L vs. D)	>0.45	NS

Abbreviations: P = Procainamide; L = lidocaine; D = diphenylhydantoin; NS = no significant difference.

Table III. Total amounts of drug administered among different groups (mg/kg)

Drug	Results*: Failure (< 4 hr.)	Results*: Success (> 4 hr.)	P value
Procainamide			
Treatment only	(8)† 16.8 ± 2.1‡	(31) 23.6 ± 2.4	= 0.1
Prophylaxis plus treatment	(6) 28.3 ± 2.8	(13) 55.8 ± 9.0§	< 0.1
Lidocaine			
Treatment only	(16) 10.8 ± 1.9	(15) 11.2 ± 2.2	> 0.5
Prophylaxis plus treatment	(7) 9.4 ± 1.1	(7) 9.9 ± 1.8	> 0.5
Diphenylhydantoin			
Treatment	(12) 12.0 ± 2.3	(14) 14.2 ± 1.5	> 0.25
Prophylaxis plus treatment	(7) 9.7 ± 1.9	(15) 17.7 ± 2.9	< 0.1

*Exact tabulation kept on all but 3 dogs not included here.
†Number of dogs in parentheses.
‡Mean ± standard error.
§High mean value results in part from total dose of 30 mg per kilogram in one dog.

and resulting toxicity from the drugs used.

Any recommendations regarding the use of PA in acute myocardial infarction are tempered by its well-known hypotensive effects when administered intravenously with any degree of rapidity, although when given slowly by this route (50 to 75 mg per minute) up to 3 Gm. have been given to humans without untoward effects. Similarly intramuscular PA administration is accompanied by minimal hypotensive effects and provides antiarrhythmic effects from 2 to as long as 10 hours.[19] PA has also been reported to have adverse hemodynamic effects in diseased human hearts.[20,21] However, in dog studies in which central and systemic circulations were studied separately a positive inotropic effect of PA was found (as opposed to lidocaine), this possibly having been masked by the fall in systemic blood pressure in the intact circulation.[14] In the normal unanesthetized dog PA has been found to have no adverse hemodynamic effects when administered intravenously slowly at dosages similar to those used clinically in man.[22]

Lidocaine, although unlikely to result in severe hypotension with intravenous ad

ministration is not without its disadvantages. Like PA it has been reported to have negative inotropic effects[11,22,24] although an intravenous bolus of 50 or 100 mg has been found to result in no significant depression of cardiac function in cardiac patients[25] Hour long infusions of 3 0 to 3 5 mg per minute have likewise been found to be well tolerated[26] Nevertheless occasionally the necessity for prolonged infusions in patients with recurring ventricular arrhythmias has resulted in excessive administration of the drug by accidental overdosage resulting in grand mal seizures[27,28] The role of lidocaine in the death of some of these critically ill patients with severe underlying heart disease cannot be stated with certainty

DPH has been found to be effective in controlling ventricular arrhythmias occurring 4 to 8 hours after experimental myocardial infarction in the dog[1] and in a variety of clinical settings[29,31] Although hypotension may result from too rapid administration intravenously this can be effectively avoided by limiting the rate in humans to 100 mg every 5 minutes[29] Hemodynamic studies in dogs have revealed minor and transient negative inotropic effects and increases in coronary blood flow[32] Therapeutic intravenous doses in man have not resulted in any adverse hemodynamic effects.[33] Although not proved superior to either of the other two agents in the current study DPH may be more useful in suppressing ventricular arrhythmias in the presence of A V block where its effect in enhancing atrioventricular conduction might make it preferable to PA and lidocaine which have less predictable effects.

Prophylactic administration was attempted with all 3 agents to determine if ventricular arrhythmias could be prevented or modified and survival rates could be increased Such was not the case which may in part be related to the timing of administration since the interaction of antiarrhythmic drugs with the cell membranes of ischemic tissue may be greater in extent than with normal tissue

Although caution must be applied in translating results in the experimental animal to man the superiority of PA in terminating ventricular arrhythmias in the present study suggests several possible clinical implications Difficult experiences in the usage of PA in general preceded the widespread establishment of coronary care units with prolonged and precise patient monitoring while the use of lidocaine more or less has paralleled the growth of such units The different settings in which these drugs have been principally used may thereby have influenced clinical impressions of their relative safety and efficacy

In addition to dose rate of administration and dose intervals other variables such as blood pH and plasma K^+ concentration may determine drug effectiveness and toxicity The patient treated in the first hour of ischemia when the risk is highest will differ from the patient seen 6 to 12 hours later as will the individual with slowly evolving or low-grade ischemia. Side effects may be significantly affected by the age of patient prior myocardial infarction or other coexistent disease or drugs. Thus, the results of this study would be more applicable to arrhythmias occurring following acute ischemia in a previously undamaged heart

While lidocaine is frequently used clinically the institution of PA therapy in ventricular arrhythmias resistant to lidocaine and for long term control of ectopic rhythms might be preferable A recent report of Koch Weser and co-workers[34] with certain advantages in design compared to previous clinical studies has indicated the feasibility of PA administration in acute myocardial infarction in the setting of a coronary unit with the close surveillance that this implies. In this study prophylaxis with PA afforded significant protection against ventricular arrhythmias but did not affect the mortality rate as compared with controls Relevant to the present study was the successful control of ventricular arrhythmias by PA in 6 of 10 patients removed from a control group because of the inability to control these arrhythmias with lidocaine. In the presence of higher degrees of atrioventricular block complicated by such arrhythmias both of these agents are contraindicated and DPH might be considered the theoretical agent of choice although firm data

on this point have yet to be reported, and the use of the transvenous pacemaker might be preferable.

Summary

Since ventricular arrhythmias complicating acute myocardial infarction in man have an uncertain course, an animal model of acute ischemia was used to compare three commonly used agents—procainamide, lidocaine and diphenylhydantoin.

A total of 150 dogs were divided into "treatment only" and "prophylaxis plus treatment" groups for each of the three agents. Twenty additional dogs served as untreated controls.

The arterial branch (left circumflex or anterior descending branch) had no effect on ultimate success in preventing ventricular fibrillation with drug therapy for at least 4 hours. Ninety per cent of untreated controls developed fatal ventricular fibrillation within 4 hours. Among the "treatment only" groups 4 hour survival with procainamide (80 per cent) was significantly higher than with lidocaine (45 per cent) or diphenylhydantoin (56 per cent). Prophylactic administration of drugs following S-T-segment elevation but preceding ventricular arrhythmias did not increase survival rate. Following acute myocardial ischemia in the previously undamaged heart, procainamide appears to afford greater protection against ventricular fibrillation than the other two agents.

The authors gratefully acknowledge the statistical advice of Mrs. Jean Chou and the secretarial services of Mrs. Barbara Collette and Mrs. Audrey Brown in the preparation of the manuscript.

Procainamide (Pronestyl), lidocaine (Xylocaine) and diphenylhydantoin (Dilantin) used in this study are generously supplied by the Squibb Institute for Medical Research, Astra Pharmaceutical Products Inc., and Parke Davis and Co., respectively.

REFERENCES

1. Harris, A. S., and Kokernot, R. H.: Effects of diphenylhydantoin sodium (Dilantin) and phenobarbital sodium upon ectopic ventricular tachycardia in acute myocardial infarction, Amer. J. Physiol. 163:505, 1950.
2. Harris, A. S., Estandia, A., Ford, T. J., Jr., and Tillotson, R. F.: Quinidine lactate and gluconate in the suppression of ectopic ventricular tachycardias associated with myocardial infarction, Circulation 4:522, 1951.
3. Harris, A. S., Estandia, A., Ford, T. J., Jr., Smith, H. T., Olsen, R. W., and Tillotson, R. F.: The effects of intravenous procaine and procaine amide (Pronestyl) upon ectopic ventricular tachycardia accompanying acute myocardial infarction, Circulation 6:551, 1952.
4. Helfant, R. H., Scherlag, B. J., and Damato, A. N.: The electrophysiological properties of diphenylhydantoin sodium as compared to procaine amide in the normal and digitalis-intoxicated heart, Circulation 36:108, 1967.
5. Hilmi, K. L., and Regan, T. J.: Relative effectiveness of antiarrhythmic drugs in treatment of digitalis-induced ventricular tachycardia, Amer. Heart J. 76:365, 1968.
6. Regan, T. J., Harman, M. A., Lehan, P. H., Burke, W. M., and Oldewurtel, H. A.: Ventricular arrhythmias and K+ transfer during myocardial ischemia and intervention with procaine amide, insulin, or glucose solution, J. Clin. Invest. 46:1657, 1967.
7. Kleinman, L. I., and Radford, E. P., Jr.: Ventilation standards for small mammals, J. Appl. Physiol. 19:360, 1964.
8. Gilmore, J. P.: Pentobarbital sodium anesthesia in the dog, Amer. J. Physiol. 209:404, 1965.
9. Weiss, A. B., Lehan, P. H., Ettinger, P. O., Moschos, C. B., and Regan, T. J.: The fate of experimentally induced coronary artery thrombosis, Amer. J. Cardiol. 23:229, 1969.
10. Kayden, H. J., Brodie, B. B., and Steele, J. M.: Procaine amide. A review, Circulation 15:118, 1957.
11. Weiss, W. A.: Intravenous use of lidocaine for ventricular arrhythmias, Anesth. Analg. (Cleveland) 39:369, 1960.
12. Lieberman, N. A., Harris, R. A., Katz, R. I., Lipschutz, H. M., Dolgin, M., and Fisher, V. L.: The effects of lidocaine on the electrical and mechanical activity of the heart, Amer. J. Cardiol. 22:375, 1968.
13. Jewett, D. E., Kishon, Y., and Thomas, M.: Lignocaine in the management of arrhythmias after acute myocardial infarction, Lancet 1:266, 1968.
14. Van Dongen, K.: The action of xylocaine on fibrillation of the heart, Arch. Int. Pharmacodyn. 96:45, 1953.
15. Austen, W. G., and Moran, J. M.: Cardiac and peripheral vascular effects of lidocaine and procainamide, Amer. J. Cardiol. 16:701, 1965.
16. Mark, L. C., Kayden, H. J., Steele, J. M., Cooper, J. R., Berlin, I., Rovenstine, E. A., and Brodie, B. B.: The physiological disposition and cardiac effects of procaine amide, J. Pharmacol. Exp. Ther. 102:5, 1951.
17. Bigger, J. T., and Heissenbuttel, R. H.: The use of procaine amide and lidocaine in the treatment of cardiac arrhythmias, Progr. Cardiovasc. Dis. 11:515, 1969.
18. Pascale, L. R., Bernstein, L. M., Schoolman, H. M., and Foley, E. F.: Intravenous procaine amide in the treatment of cardiac arrhythmias, Amer. Heart J. 48:110, 1954.
19. Easelberg, C. D., and Lipkin, M.: The intramuscular administration of procaine amide, Amer. Heart J. 44:781, 1952.
20. McClendon, R. L., Hansen, W. R., and Kling-

mon J M Hemodynamic changes following procaine amide administered intravenously Amer J Med Sci 222:375 1951
21 Harrison D C, Sprouse J H and Morrow A G The antiarrhythmic properties of lidocaine and procaine amide Circulation 28:486 1963
22 O Rourke R A, Bishop V S, Stone H L and Rapaport E. Lack of effect of procaina mide on ventricular function in conscious dogs, Amer J Cardiol 23:238 1969
23 Nelson, D and Harrison D C. Comparison of the negative inotropic effects of procaina mide lidocaine and quinidine, Physiologist 8:241 1965
24 Bacaner M Quantitative comparison of bretylium with other antifibrillatory drugs, Amer J Cardiol 21:501 1968
25 Schumacher R. R Lieberson A. D Childress, R. H and Williams, J F Hemodynamic effects of lidocaine in patients with heart disease, Circulation 37:965 1968
26. Grossman J I Cooper J A and Frieden J Cardiovascular effect of infusion of lidocaine on patients with heart disease Amer J Cardiol 24:191 1969
27 Crampton R S. and Oriscello, R. G Petit and grand mal convulsions during lidocaine treat ment of ventricular tachycardia J.A.M.A. 204:109 1968.
28 Julian, D G., and Oliver M F: Acute myocardial infarction Baltimore, 1968, The Williams & Wilkins Company p. 113
29 Mercer E. N and Osborne J A: The current status of diphenylhydantoin in heart disease, Ann. Intern. Med 67:1084 1967
30 Bigger J T Schmidt D H and Kutt, H. Relationship between the plasma level of diphenylhydantoin and its cardiac antiarrhythmic effects, Circulation 38:363 1968.
31 Helfant, R H Scheuffert G. W Patton, R. D Stein, E. and Damato, A. N The clinical use of diphenylhydantoin (Dilantin) in the treat ment and prevention of cardiac arrhythmias AMER HEART J 77:315 1969
32. Gupta D N., Unal M O Bashour F A., and Webb W R: Effects of diphenylhydantoin (Dilantin) on peripheral and coronary circulation and myocardial contractility in the experimental animal Dis. Chest 51:248, 1967
33 Conn R. D Kennedy J W and Blackmon, J R. The hemodynamic effects of diphenylhydantoin AMER HEART J 73:500, 1967
34 Koch Weser J Klein S. W Foo-Canto, L. L, Kastor J A and DeSanctis, R. W: Antiarrhythmic prophylaxis with procainamide in acute myocardial infarction, New Eng J Med. 281:1253 1969

Effects of ouabain on splanchnic hemodynamics in the rhesus monkey

Linda L. Shanbour Ph.D
Eugene D. Jacobson M.D
Guenther F. Brobmann M.D
Lerner B. Hinshaw Ph.D
Oklahoma City Okla

Numerous studies have been conducted to evaluate the cardiotonic effects of ouabain in the dog and the human being. As a digitalizing drug, ouabain is generally considered to exert a positive inotropic effect on heart muscle by increasing the rate at which tension is developed.[1-3]

Over four decades ago, digitalis was reported to decrease cardiac output in the nonfailing dog heart. Subsequently investigators attributed this decrease in cardiac output to a decrease in venous return produced by a direct action on capacitance vessels of the circulation.[4-] Although similar results were reported for normal human subjects by some investigators,[8-10] others[11] published conflicting findings, i.e. no significant reduction in cardiac output or in hemodynamic changes in normal human subjects. Initially the splanchnic region was implicated as the site of pooling in the dog.[12-1] However Harrison and associates, with the use of electromagnetic blood-flow transducers and pressure transducers in the fully digitalized dog without arrhythmias, reported no significant changes in portal venous pressure, organ weights, or liver blood volume. They concluded that the major splanchnic event induced by ouabain was arteriolar vasoconstriction since arterial pressure increased in the face of a small decline in mesenteric and splenic arterial blood flow.

The finding that cardiac glycoside constricts splanchnic arterioles has important implications, if one can extrapolate canine data to man.[16] The purpose of the present investigation was to determine the splanchnic hemodynamic responses of a subhuman primate (rhesus monkey) to fully digitalizing doses of ouabain as well as to higher doses producing cardiac arrhythmias.

Methods

Nine male rhesus monkeys, weighing between 4.0 and 6.2 kilograms, were anesthetized with sodium pentobarbital (30 mg per kilogram). A laparotomy was performed and a noncannulating electromagnetic blood-flow transducer (Micron) was placed around the superior mesenteric artery before its first bifurcation. The transducer was connected to an electromagnetic blood-flow amplifier (Biotronix). Portal

From the Departments of Physiology and Biophysics, Medicine, and Surgery, University of Oklahoma Medical Center, Oklahoma City, Okla.

This research was supported in part by Department of Defense Grant N00014-68-A-0496 and by United States Army Grant DADA-49-C9035.

Received for publication May 12, 1970.

Reprint requests to: Linda L. Shanbour, Ph.D., Department of Physiology and Biophysics, University of Oklahoma Medical Center, 800 Northeast Thirteenth St., Oklahoma City, Okla. 73104.

Vol. 81, No. 4, pp. 511-515, April 1971

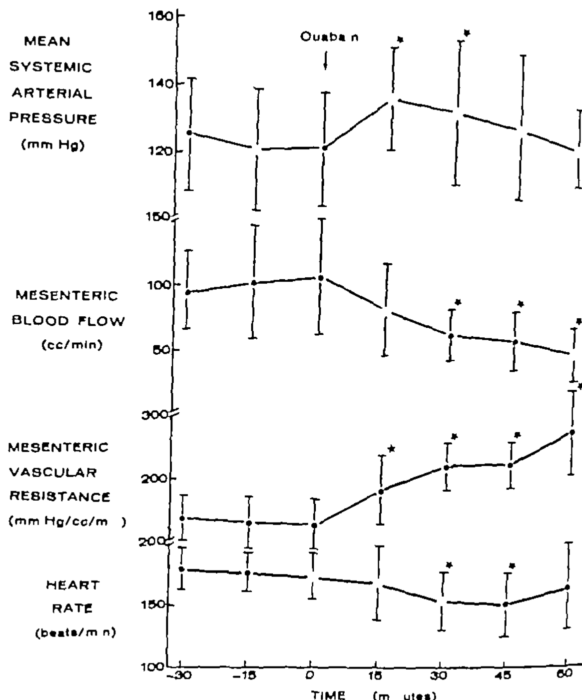


Fig. 1 Mean systemic arterial pressure mesenteric blood flow mesenteric vascular resistance, and heart rate in 5 dogs receiving a fully digital zing dose of ouabain V lues shown as means ± S.D Asterisk indicates significant difference from control values ($p < 0.05$)

vein pressures were monitored via a catheter introduced into an accessory splenic vein and another catheter was inserted into a femoral artery These catheters were connected to pressure transducers (Sanborn) Electrocardiographic (ECG) recordings were obtained from limb leads. Systemic arterial and portal venous pressures mesenteric blood flow and the cardiogram were recorded on a four-channel direct writing polygraph (Sanborn) A maximal therapeutic dose (20 to 35 µg per kilogram) of ouabain was injected through a femoral vein catheter in all 9 monkeys. In 4 monkeys cardiac arrhythmias developed shortly after injection of the drug Statistical significance of observed changes was assessed using Duncan s New Multiple Range Test.[11]

Results

Five animals which received the maximal therapeutic dose showed the following ECG

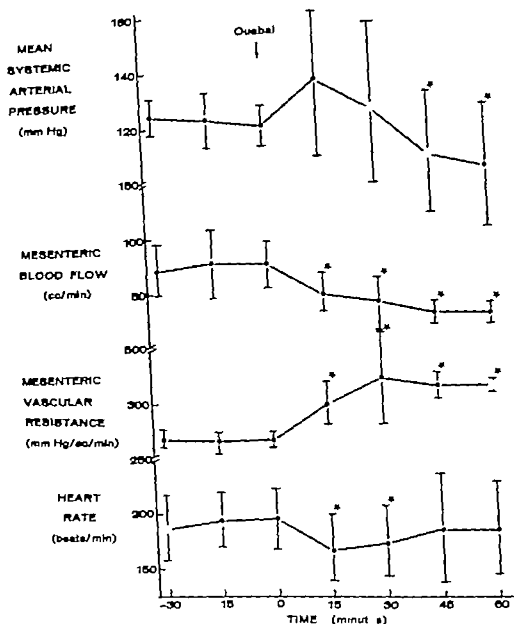


Fig. 2 Mean systemic arterial pressure, mesenteric blood flow mesenteric vascular resistance and heart rate in 4 dogs receiving dose of ouabain that produced arrhythmias. Values shown as means ± S.D Asterisk indicates significant difference from control values ($p < 0.05$)

changes S-T depression T wave elevation and/or slowing of heart rate with no arrhythmias. Fig 1 presents the hemodynamic responses of these monkeys. The mean systemic arterial pressure responded inconsistently to ouabain In 3 animals the pressure increased in one no change occurred and in one the pressure decreased Ouabain elicited no changes in portal venous pressure. In all 5 monkeys, mesenteric blood flow decreased (significant at 30, 45 and 60 minutes) and mesenteric vascular resistance increased (significant at 15 30 45 and 60 minutes) The mean heart rate was significantly decreased at 30 and 45 minutes.

Fig 2 shows the hemodynamic responses of the 4 monkeys given ouabain in a dosage

sufficient to produce arrhythmias The results are essentially similar to those obtained in the first group No over-all significant change was found in portal venous pressure The mean systemic arterial pressure was significantly decreased at 45 and 60 minutes. In all 4 animals mesenteric blood flow decreased (significant at 15 30 45 and 60 minutes) and mesenteric vascular resistance (significant at 15 30 45 and 60 minutes) increased Likewise heart rate decreased in all 4 cases (significant at 15 and 30 minutes)

Discussion

The finding that fully digitalized monkeys and excessively digitalized monkeys showing arrhythmias respond with a significant decrease in mesenteric blood flow and a significant increase in mesenteric vascular resistance confirms canine data obtained by Harrison and associates[19] as well as the early findings of Rothlin[22] who also reported increased mesenteric vascular resistance with digitalis Moreover it lends credence to the suggestion of other workers[23,24] that glycoside treatment may lead to chronic ischemia of the gut

The clinical implications of mesenteric arterial constriction with cardiac glycoside in animals with healthy hearts have been discussed previously[19] It is generally held that prophylactic use of digitalis is safe in patients in shock without heart failure In view of the present evidence however we believe this practice may be hazardous Since these patients already have poor mesenteric perfusion the superimposition of glycoside constriction may precipitate a fatal state of nonocclusive mesenteric ischemia.

Our results do not indicate whether the increase in mesenteric vascular resistance is an isolated regional hemodynamic response to ouabain or a general peripheral vascular phenomenon Earlier reports indicated that total peripheral resistance increased with ouabain[5,7,9,11] The findings of the present report were obtained in normotensive primates and may not be applicable in the human in shock whose splanchnic perfusion is already compromised Further more there may be a therapeutic advantage in accepting some increase in mesenteric vascular resistance as the price for improved cardiorenal blood flow in the shock patient. There are however limits to this bargain since nonocclusive mesenteric ischemic disease is a lethal state in man

Summary

When the effects of ouabain on splanchnic hemodynamics of the anesthetized monkey are evaluated the major events were found to be a decrease in mesenteric blood flow and an increase in mesenteric vascular resistance Implications of these findings are that use of cardiac glycosides may be contraindicated in clinical states characterized by low blood flow to the splanchnic region.

The authors are indebted to Mr Alvin C. K. Chang Mr R. T Brantley and Mrs. Linda T Archer for technical assistance.

REFERENCES

1 Wiggers, C. J., and Stimson, B Studies on the cardiodynamic actions of drugs. III The mechanism of cardiac stimulation by digitalis and g strophanthin, J Pharmacol Exp. Ther 30 251 1927
2 Siegel J H and Sonnenblick, E. H Isometric time-tension relationships as an index of myocardial contractility Circ. Res. 12:597 1963.
3 Harrison, T R., and Leonard B W The effect of digitalis on the cardiac output of dogs and its bearing on the action of the drug in heart disease J Clin. Invest. 3:1 1926
4 Cohn A. E. and Stewart, H J The relation between cardiac size and cardiac output per minute following administration of digitalis in normal dogs, J Clin. Invest. 7:53 1929
5 Dock, W and Tainter M L. The circulatory changes after f ll therapeutic doses of digitalis with a critical discussion of views on cardiac output, J Clin. Invest. 8:467 1930
6. Katz, L. N Rodbard S Friend M and Rottersman W The effect of digitalis in the anesthetized dog I Action on the splanchnic bed J Pharmacol Exp. Ther 62 1 1938.
7 Cotten M deV and Stopp P E. Action of digitalis on the nonfailing dog heart, Amer J Physiol 192:114 1958.
8. Stewart, H. J and Cohn, A. E. Studies on the effect of the ction of digitalis on the output of blood from the heart. 1 The effect on the output in normal human hearts. 2. The effect on the outp t of hearts in heart failure with congestion in human beings, J Clin. Invest. 11:917 1932.
9 B ng R. J Maraist, F M Dammann, J F Draper A. Heimbecker R., Daley R., Gerard R. and Calazel P Effect of strophanthus on coronary blood flow and cardiac oxygen consumption of normal and failing h man hearts, Circulati n 2:513 1950
10. Williams, M H., Zohman, L. R. and Ratner

A. C. Hemodynamic effects of cardiac glycosides on normal human subjects during rest and exercise, J Appl. Physiol. 13:417 1958

11. Dresdale, D T Yuceoglu, Y Z., Michtom, R. J Schultz, M and Lunger M Effects of lanatoside C on cardiovascular hemodynamics—Acute digitalizing doses in subjects with normal hearts and with heart disease without failure, Amer J Cardiol. 4:88 1959

12. Selzer A., Hultgren, H. N Ebnother C. L. Bradley H W and Stone, A. O Effect of digoxin on the circulation in normal man, Brit. Heart J 21:335, 1959

13. Talater M L., nd Dock, W Further observations on the circulatory actions of digitalis and strophanthin with special reference to the liver and comparisons ith histamine and epinephrine, J Clin. Invest. 8:485 1930.

14. Rodman, T nd Pastor B. H. The hemodynamic effects of digitalis in the normal and diseased heart, Amer. Heart J 65:564 1963

15. Braunwald, E. Mason, D T and Ross, J Jr Studies on the cardiocirculatory actions of digitalis, Medicine 44:233, 1965.

16. Lyon, A. F and DeGraff A. C. Reappraisal of digitalis. II. Hemodynamic effects of the cardiac glycosides, Amer. Hear J 72:565, 1966.

17 Nadler J E Berger A. R and Ballinger J Action of ouabain on the splanchnic circulation in the dog J Lab. Clin. Med. 25:337 1940.

18. Ross, J J Braunwald, E., and Waldhausen, J A.: Studies on digitalis. II Extracardiac effects on venous return and on the capacity of the peripheral vascular bed, J Clin. Invest. 39:937 1960.

19 Harrison, L. A., Blaschke, J., Phillips, R. S., Price, W E., Cotten, M deV and Jacobson, E. D.. Effects of ouabain on the splanchnic circulation, J Pharmacol. Exp. Ther 169:321 1969

20. Jacobson, E. D Should digitalis be used in shock. Medical Counterpoint, 1969 p. 69

21. Steel, R. G. D and Torrie, J H. Principles and procedures of statistics, New York, 1960, McGraw Hill Book Company Inc., pp. 99 and 107

22. Rothlin, E. On the pharmacology of squill, Sch eiz. Med. Wschr 49 1171 1927

23. Gazes, P C., Holmes, C. R., Moseley V and Pratt Thomas, H. R. Acute hemorrhage and necrosis of the intestine associated with digitalization, Circulation 23:358, 1961.

24. Ferrer M. I Bradley S. E., Wheeler H. O Enson, Y Preisig R., and Harvey R. M. The effect of digoxin in the splanchnic circulation in entricular failure, Circulation 32:524 1965

Myocardial and serum lactate changes during isoproterenol-induced infarction

Robert F Lutmer Ph D
Bernard C Wexler Ph D
Cincinnati Ohio

Severe myocardial infarction can be induced in rats by two subcutaneous injections of the potent beta adrenergic stimulating agent isoproterenol [1,2] During the acute necrosis phase we have observed marked increases in serum enzymes e g creatine phosphokinase glutamic oxaloacetic and glutamic pyruvic transaminases, and lactic dehydrogenase [3,4] glucose lipids and lipoproteins [3] adrenal steroids,[4] and hepatic lipids.[5] During the myocardial repair phase all of these returned to normal levels

All of our metabolic measurements indicate that the induction of myocardial damage is of rapid onset, becoming apparent within 30 min of the first injection of isoproterenol [6,7] Special histochemical tests demonstrate that the anoxic or ischemic foci in the myocardium change from normal aerobic to anaerobic metabolism which leads to glycolysis and increased acidophilia.[7] Our investigations indicate that there is partial recovery from the intense myocardial stimulatory effects of the first injection of isoproterenol [6,7] The second injection of isoproterenol consummates the production of severe myocardial necrosis and is overwhelming since there is little or no evidence of alternating aerobic and anaerobic metabolism but, rather overt and widespread necrosis.[7]

Myocardial anoxia or ischemia leads to glycolysis, acidosis, electrolyte shifts, edema, and the accumulation of pyruvate and lactate in the heart and serum [8-11] Thus, the level of serum lactate may be used as an index of myocardial ischemia. In fact, the relative effectiveness of myocardial vascular supply can be approximated by challenging the patient with isoproterenol and determining the capacity of the heart to respond to this increased work load in terms of serum lactate levels [11,12] In this same connection we induced myocardial infarcts in healthy male Sprague Dawley rats with isoproterenol and attempted to trace the temporal development of episodes of the drug induced ischemia by measuring both the cardiac and serum lactate levels at hourly intervals, following each of two injections of isoproterenol

From the May Institute for Medical Research of the Jewish Hospital and Department of Pathology University of Cincinnati, College of Medicine Cincinnati, Ohio.
Supported, in part, by grants from the Southwestern Ohio Heart Association, the National Heart Institute, National Institutes of Health (Grants HE-6315 and HE-8868) and by General Research Support Grant (RR-5633) from the National Institutes of Health, United States Public Health Service. Dr Wexler is supported by the Research Career Award Program (HE-K3-1734) National Heart Institute National Institutes of Health, United States Public Health Service.
Received for publication May 14, 1970.
Reprint requests to Dr Robert F Lutmer May Institute for Medical Research, 421 Ridgeway Avenue Cincinnati, Ohio 45229

April 1971 Vol. 81 No. 4, 516-520

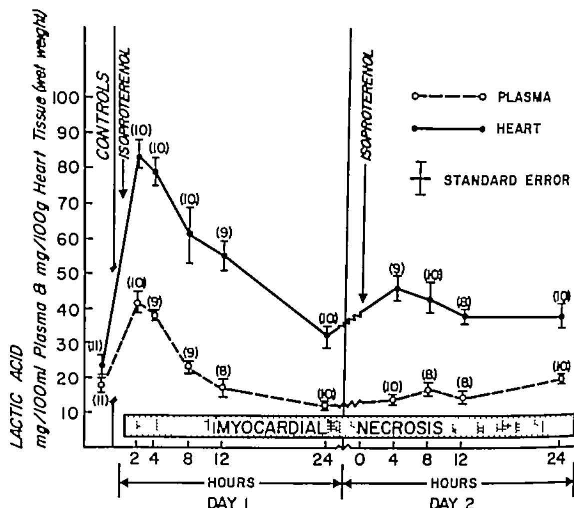


Fig 1 Changes in heart and plasma lactic acid levels of male Sprague-Dawley rats at various time intervals after two injections of isoproterenol spaced 24 hr apart

which does not make efficient use of cardiac glycogen Pyruvic acid metabolism is blocked and excess lactic acid accumulates in the ischemic areas Clinicians have used myocardial or serum lactic acid levels as an index of myocardial ischemia in cases of angina and coronary heart disease[1, 13] Further isoproterenol has been used to deliberately provoke myocardial ischemia due to increased cardiac work[13] This, in turn elicits increased cardiac lactic acid The degree of increase of lactic acid in the heart or blood is used as an index of the severity of myocardial ischemia or coronary vascular disease Isoproterenol is a potent beta-adrenergic stimulating agent which causes decreased peripheral resistance and increased cardiac output. The dose of isoproterenol used by the authors causes such intense ventricular contraction and increased cardiac output that the myocardium promptly outstrips the ability of the coronary arteries to provide adequate blood flow the myocardium becomes ischemic or relatively anoxic, and necrosis ensues.

The very prompt increase observed here in both cardiac and plasma lactic acid demonstrates the nature of the rapid onset of myocardial ischemia following treatment with isoproterenol In all of our other studies we have found a similar increase in serum enzymes lipids, glucose lipoproteins corticosterone and other metabolic indices promptly following the first injection of isoproterenol[3, 7] It is during this period of the early manifestations of marked systemic metabolic alterations that we find beginning evidence of myocardial edema and degenerative change[6, 7, 11, 14] The relative dampening of myocardial responsiveness expressed in terms of cardiac and plasma lactic acid following the second injection of isoproterenol also coincides with our other ancillary studies, e.g changes in enzymes, gluco[illegible] [illegible], and

Methods

Adult, male, Sprague Dawley rats were used in this experiment. These animals were maintained in our Research Animal Colony for 30 days under controlled conditions of temperature, humidity and light prior to their use. The animals were given water *ad libitum* and were fed a commercial rat chow (Teklad) which has a relatively low fat content (4 per cent).

A total of 170 male rats, ranging from 320 to 375 grams were randomly divided into 11 groups. The first group (10 rats) received no treatment and served to establish base-line levels for myocardial and serum lactic acid. The remaining 110 animals were injected subcutaneously with isoproterenol, i.e. 50 mg per 100 Gm of body weight. Following the first injection of isoproterenol, 40 animals were put to death at 4, 8, 12 and 24 hours later, i.e., 10 animals per each time interval. The next day, the same dose of isoproterenol was given to the remaining animals and these were also put to death 4, 8, 12 and 24 hours later (10 animals per group). A special pool of isoproterenol treated animals was provided to insure an adequate number of surviving animals for each time interval, i.e., at this dose level of isoproterenol, maximal myocardial infarction is induced and approximately 50 per cent of the treated animals die.

Just prior to sacrifice the animals were anesthetized lightly with Seconal and a heparinized blood sample was taken from the inferior vena cava of each animal. The thorax was exposed and the entire heart was quickly removed and frozen in liquid nitrogen. Both serum and myocardial lactic acid content were determined by Hohorst's method,[16] i.e., expressed as milligrams of lactic acid per 100 Gm. of heart tissue wet weight and per 100 ml. of serum.

In ancillary experiments, male rats of the same weight range were subjected to the same regimen of isoproterenol injections. Their hearts were removed at similar time intervals and stained with hematoxylin and eosin and acid fuchsin to demonstrate any early evidence of damage due to myocardial ischemia, e.g., acidophilia, glycolysis, and myocardial necrosis on a histopathologic basis.

Results

The first injection of isoproterenol produced very definite indications of intense myocardial stimulation, e.g., tachycardia, deep and rapid respiration, marked prostration, and a high mortality rate. There was a prompt and significant rise in both myocardial and serum lactic acid levels within two hours of the first injection of isoproterenol (Fig. 1). Myocardial lactate levels remained abnormally elevated throughout the course of the experiment, although they were lowered, almost to normal, 24 hours after the first injection of isoproterenol (Fig. 1). Serum lactate levels followed a similar pattern of dramatic increase followed by a decline but they were restored to normal within 8 to 12 hours following the first injection of isoproterenol.

On the second day (Day 2), the second injection of isoproterenol also caused intense tachycardia, prostration, and rapid respiration. However, despite all of these signs of myocardial failure, the plasma lactate levels showed little or no response and cardiac lactate levels showed only a slight, evanescent rise.

Histopathologically, the hearts of the isoproterenol treated animals manifested intense positive fuchsinophilia following the first injection of isoproterenol reaching a peak intensity of staining within 2 to 4 hours post injection (Fig. 2). This positive fuchsinophilia promptly faded and did not reappear until 2 to 4 hours after the second injection of isoproterenol. At this time, the degree of positive fuchsinophillia was in no way comparable to that observed 2 to 4 hours after the first injection. Positive fuchsinophilia is indicative of focal tissue acidity, i.e., increased glycolysis, due to changes in focal myocardial metabolism from aerobic to anaerobic metabolism.[16]

Discussion

These findings indicate that isoproterenol produced prompt and intense myocardial anoxia or ischemia. When the myocardium becomes ischemic or anoxic, anaerobic rather than aerobic metabolism supervenes in the areas of ischemia in order to provide energy for contraction. Glycolysis proceeds through the Embden-Meyerhof pathway

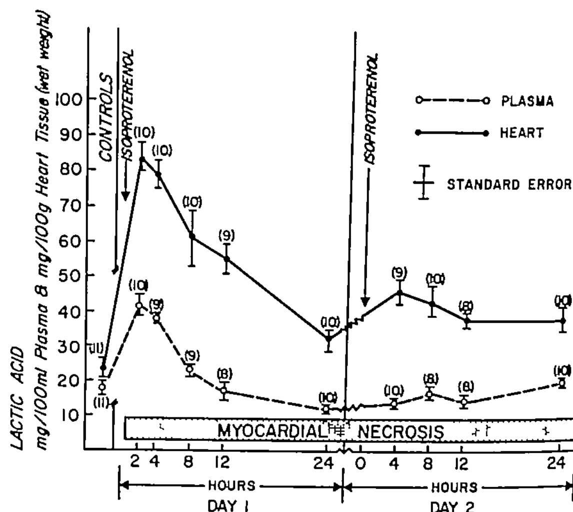


Fig 1 Changes in heart and plasma lactic acid levels of male Sprague-Dawley rats at various time intervals after two injections of isoproterenol paced 24 hr apart.

which does not make efficient use of cardiac glycogen Pyruvic acid metabolism is blocked and excess lactic acid accumulates in the ischemic areas. Clinicians have used myocardial or serum lactic acid levels as an index of myocardial ischemia in cases of angina and coronary heart disease[11, 12] Further isoproterenol has been used to deliberately provoke myocardial ischemia due to increased cardiac work.[13] This in turn elicits increased cardiac lactic acid The degree of increase of lactic acid in the heart or blood is used as an index of the severity of myocardial ischemia or coronary vascular disease. Isoproterenol is a potent beta adrenergic stimulating agent which causes decreased peripheral resistance and increased cardiac output. The dose of isoproterenol used by the authors causes such intense ventricular contraction and increased cardiac output that the myocardium promptly outstrips the ability of the coronary arteries to provide adequate blood flow the myocardium becomes ischemic or relatively anoxic, and necrosis ensues.

The very prompt increase observed here in both cardiac and plasma lactic acid demonstrates the nature of the rapid onset of myocardial ischemia following treatment with isoproterenol In all of our other studies we have found a similar increase in serum enzymes lipids glucose lipoproteins corticosterone and other metabolic indices promptly following the first injection of isoproterenol[1, 7] It is during this period of the early manifestations of marked systemic metabolic alterations that we find beginning evidence of myocardial edema and degenerative change[4, 7, 15, 16] The relative dampening of myocardial responsiveness expressed in terms of cardiac and plasma lactic acid following the second injection of isoproterenol also coincides with our other ancillary studies, e.g changes in enzymes, glucose, lipids, and

A microangiographic study of myocardial infarction

An experimental study in the rabbit with a comparison with human autopsy material

O. Hassler, M.D.
Umeå, Sweden

It has long been known that the size and location of a myocardial infarction is not only dependent on the occlusion of one *feeding artery* but on a number of factors that at present are partly obscure, i.e., the status of the whole vascular system of the heart and the capacity of the collaterals within and outside the heart.[1] The vascular contribution to the important process of healing is also incompletely known, but knowledge of it may be of interest when efforts are made to improve the prognosis and manage complications. Microangiography, which makes the microangioarchitecture clearly visible, *does not seem to* have been applied previously to the heart in the case of myocardial infarction. The present study, in which experimental myocardial infarctions in the rabbit were examined by microangiography, was started with the hope that the findings by this method would throw more light on these important problems. For comparison, human hearts with infarctions were also examined in a similar way.

Materials and methods

Rabbit experiments. In 20 rabbits myocardial infarctions were induced by ligating the descending branch of the left coronary artery as proximally as possible. Three animals died in connection with the operation and were excluded. The remaining 17 were killed 1, 2, 4, 6, 7, 10, 12, 14, 16, 20, 25, 30, 40, 60, 90, 120, and 180 days after the operation. Another 5 rabbits belonging *to the same litters served as controls. In all* the animals the chest was opened and x-ray contrast medium was injected into the ascending aorta in a way similar to that described in a previous work.[2] The heart was fixed in formalin and cut into 1 mm thick slices in a plane at right angles to its axis. The microangiographic examination *was performed in the same way as in a* previous study.[3] Histological examinations using van Gieson's stain were made of all slices with infarctions.

Human autopsy material. At the Departments of Pathology of the University Hospital in Umeå and of the County Hospital in Falun, 14 autopsy cases were selected from those corpses *that underwent examination* less than 36 hours post mortem. Nine had the clinical diagnosis of myocardial infarction (Table I) and five were controls. Only infarction cases with marked acute symptoms, typical changes on the electrocardiogram, granulocytosis, and a typical increase in the glutamic oxaloacetic

From the Department of Pathology, University of Umeå, Umeå, Sweden.
Supported by Grant B70-12X-961-06 from the Swedish Medical Research Council.
Received for publication June 8, 1970.
Reprint address: Dr. O. Hassler, Department of Pathology, University of Umeå, S-901 87 Umeå 6, Sweden.

Summary

Adult male Sprague Dawley rats were given two daily injections of the potent beta adrenergic stimulating agent, isoproterenol Cardiac and plasma lactic acid levels were measured as an index of the degree of myocardial ischemia induced by isoproterenol The first injection (Day 1) produced a prompt increase in both lactic acid levels which returned to normal in the blood but remained elevated in the heart tissue The second injection (Day 2) did not cause any unusual increase in cardiac or plasma lactic acid levels Histochemical fuchsinophilia used as an index of glycolysis acidosis or lactic acid coincided with the pattern of lactic acid changes determined chemically These findings suggest that the myocardium of these animals has some capacity to make metabolic adjustments to compensate for the initial duress of isoproterenol stimulation However the second injection appears to be overwhelming causing irreversible damage which progresses unabated to overt necrosis

The authors wish to thank Miss Barbara Cincush for her technical assistance.

REFERENCES

1 Rona, G Chappel C. I Balazs, Jr and Gaudry R. An infarct like myocardial lesion and other toxic manifestations produced by isoproterenol in the rat Arch. Path. (Chicago) 67:443 1959
2. Wexler B C. and Kittinger G W Myocardial necrosis in rats. Serum enzymes, adrenal steroids and histopathological alterations, Circ. Res. 13:159 1963
3 Wexler B C. Judd J T and Kittinger G W Myocardial necrosis induced by isoproterenol in rats, Angiology 19:665 1968
4. Wexler B C and Kittinger G W Steroids produced in vitro by adrenal glands by normal and arteriosclerotic rats during and after drug induced myocardial necrosis, Circ. Res. 16:322, 1965
5 Judd J T and Wexler B. C. Acute changes in liver lipids during myocardial infarction induced by isoproterenol Proc. Soc. Exp. Biol. Med 130:1302 1969
6 Wexler B C. Serum creatine phosphokinase activity following isoproterenol induced myocardial infarction in male and female rats with and without arteriosclerosis, AMER. HEART J 79:69 1970.
7 Wexler B C. and Judd J T Acute myocardial histopathologic changes in arteriosclerotic rats following isoproterenol induced infarction, Brit. J Exp. Path. 51:646, 1970.
8. Bing R. J Cardiac metabolism, Physiol. Rev 45:171 1965
9 Scheuer J Myocardial metabolism in cardiac hypoxia Amer J Cardiol 19:385 1967
10. Gudbjarnason, S. Braasch, W Cowan, C. and Bing R. J Metabolism of infarcted heart muscle during tissue repair Amer J Cardiol. 22:360 1968.
11 Herman M V Elliott W C and Gorlin, R. An electrocardiographic anatomic and metabolic study of zonal myocardial ischemia in coronary heart disease, Circulation 35:834 1967
12. Bourassa, M G Campeau L. Bois, M A., and Rico O Myocardial lactate metabolism at rest and during exercise in ischemic heart disease, Amer J Cardiol 23 771 1969
13 Elliott W C and Gorlin R. Isoproterenol in treatment of heart disease. Hemodynamic effects n circulatory failure, J.A.M.A. 197:315 1966
14. Hohorst, H J *In* Bergmeyer H. U editor Methods of enzymatic analysis, New York, 1965 Academic Press, Inc.
15 Judd J T and Wexler B C. Myocardial connective tissue metabolism n response to injury Circ. Res. 25:201 1969
16 Judd J T and Wexler B C. Myocardial connective tissue metabolism in response to injury II Investigation of the mucopolysaccharides involved in isoproterenol-induced necrosis and repair in rat hearts, Circ. Res. 26:101 1970



Fig. 1 Microangiograms from 1 mm thick slices through the anterior wall of the left ventricle of rabbit hearts. The slices were cut in a plane forming right angle with the longitudinal axis of the heart. Epicardium upward and endocardium with the lumen downward. *A*, Normal angioarchitecture, with large arteries in the epicardium sending out penetrating branches directed towards the lumen. *B*, Seven-day-old infarction. The vessels show irregular and incomplete filling within the infarcted area. Some slender newly formed vessels occur at the border on the right and also downward. *C*, Thirty-day-old infarction. Several coarse-calibered vessels have circular course in the thinned ventricular wall. (× 11.)

in which branches from large trunks in the epicardium traversed the wall of the heart in a direction roughly at right angles to the endocardial surface During the first four days the area of infarction could only irregularly and incompletely be filled with x-ray contrast medium. The first newly formed vessels could be discovered after

Table I Some clinical and autopsy data on the human material (Cases 10 to 14 were control material)

Case No	Age (yr)	Sex	Main disease	Heart weight (grams)	Enlargement of left side of heart	Location of the occlusion	Age of infarction (days)
1	4	M	Myocardial infarction	480	+	L.D C.A.	7
2	58	M	Myocardial infarction	530	+	L.D C.A.	1
3	59	M	Myocardial infarction	670	+	L.D C.A.	4
4	63	M	Myocardial infarction	450	+	L.D C.A.	2
5	67	F	Myocardial infarction	410	+	L.D C.A.	20
6	77	M	Myocardial infarction	440	+	L.D C.A	210
7	77	F	Myocardial infarction	500	+	R.C.A.	30
8	78	M	Myocardial infarction	860	+	L.D C.A.	12
9	82	F	Myocardial infarction	390	+	R C.A.	45
10	34	F	Astrocytoma	230	−		
11	38	M	Cerebellar hemangioblastoma	250	−		
12	53	M	Gastric adenocarcinoma	330	−		
13	64	M	Adenocarcinoma of colon	320	−		
14	84	F	Adenocarcinoma of the breast	290	−		

L D C A. = Left descending coronary artery R.C.A. = right coronary artery

transaminases were selected In addition Cases 5 and 9 were shown to have had an additional infarction a few days before death Cases 6 and 7 died of very acute heart failure that might have been a new infarction These recent infarctions seemed to be of little practical importance in the present study because the filling of x ray contrast medium in large parts of the autopsy material and especially the recent infarctions (see Results) was poor As will be apparent from Results only positive findings i e vascular neoformations in infarctions older than one week could be reliably recorded in the autopsy material The controls had had no symptoms of any myocardial infarction

In all cases a cannula was inserted into the left ventricle through the ascending aorta which was ligated distally like the pulmonary veins, so that there was no leakage, when x ray contrast medium was injected into the left ventricle All air was removed from the left ventricle and atrium before the injection was started X ray contrast medium was injected in the same way as in a previous work.[3] The heart was fixed in formalin and cut into 1 mm thick slices in a plane at right angles to the axis of the heart. The slices were examined by microradiography[3] Areas with obvious or suspected infarction were embedded in paraffin and sections stained with van Gieson's stain or phosphotungstic acid hematoxylin were produced The age of the infarction determined histologically by the criteria given by Mallory and associates[4] showed good agreement with the clinical history In Cases 5 and 9 there were also additional infarctions approximately a few days old In Cases 6 and 7 no signs of recent infarction could be detected

Results

Rabbit The general condition of the rabbits seemed to be little influenced by the operation The operation wounds healed with no visible complications.

The histologic examination showed that the infarctions varied in size between approximately 5 and 20 million μ^3 In the pericardium there were often signs of a slight inflammation with small fibrinous or fibrous adhesions at the site of the operation but no other complications could be discovered The x ray contrast filling was observed to be practically 100 per cent in the capillaries in all cases except in the infarcted areas during the first 10 days.

The microangiographical examination showed that the normal heart had a characteristic regular vasculature (Fig 1 *A*)



Fig. 1. *A*. Case 1. Solitary vessels filled with x-ray contrast medium in a 4-day-old infarct. *B*. Case 6. In the lower half of the figure there is an infarction that is about 7 months old. It is poor in vessels. (× 11.)

40 days (Fig. 1, *C*). No vascular neoformation was ever observed in the thebesian vessels.

Human material. The normal angioarchitecture of the human heart is demonstrated in Fig. 2, *A*. It resembled that of the rabbit heart (see above). In infarct Cases 1 through 4 and 8 the x-ray contrast filling was always incomplete and irregular, with approximately 25 to 80 per cent filling of the capillaries and sometimes extravasations of x-ray contrast medium. In the control cases (Nos. 10 to 14, Table I) and in the late infarction cases (Nos. 5 through 7 and 9) the filling of the capillaries with x-ray contrast medium was complete in at least 60 per cent of the tissue volume. The description must therefore be focused on the positive findings of vascular neoformation. In the infarctions estimated to be 1, 2, and 4 days old, respectively, there was no such positive finding. The area of infarction practically was not filled in any of the three cases. Only solitary filled vessels could be discerned sometimes (cf. Fig. 3, *A*).

After 7 to 30 days there was a strong ingrowth of wide vessels (Fig. 2, *B* and *C*) from the lateral borders of the infarction toward its center. The vessels always took a circular direction, like those in the rabbit, parallel with the endocardial surface. The number and caliber of the newly formed vessels were largest in Cases 5, 7, 8, and 9. The centers of the infarctions in Cases 1, 5, and 8 were not vascularized. The infarcted areas of Cases 6, 7, and 9 were completely vascularized. In Case 6, there was a marked reduction in the number of newly formed vessels (Fig. 3). No vascular neoformation was ever observed in the thebesian vessels. In Cases 6, 7, and 9 there were exceptionally many and wide collateral arteries several centimeters from the infarction.

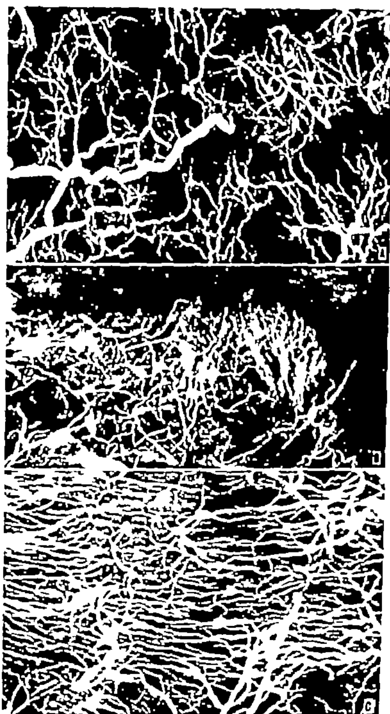


Fig. 2 Microangiograms similar to those i Fig 1 but from h man hearts. A Normal angioarchitecture, Case 13 *B* Infarction estimated to be 7 days old C o 1 The vessels are practically not filled within the infarcted area (upward and to the right) A dense net of slender newly formed vessels occur at the border of the infarction. *C* Infarction that was approximately 30 days old, Case 7 The vessels are much more numerous and coarse-calibered than in Fig 1 *C* but have a sim la course. Newly formed vessels occur lso in the border of the myocardium (upward) (× 11)

5 days. The new vessels ran from the lateral borders of the infarction (Fig 1 *B*) toward its center They had a circular direction in slices of the heart cut at right angles to its axis and thus quite a different appearance from those in the normal heart. The center of the infarction was not vascularized until after 10 days. The number of newly formed vessels was greatest in the animals killed 10 to 20 days after the ligation After 20 days the number of newly formed vessels was gradually decreased but the caliber of the individual vessels was increased The maximum caliber was obtained after 20 to

lowing the ligation were probably too small and developed too late to cause any collateral circulation of importance.

The microangiographical examinations demonstrated that the number of newly formed vessels was much greater in the human than in the rabbit hearts, apparently partly because the infarctions were larger in the former. The centers of the infarctions were also vascularized later in the human than in the rabbit material. This was apparently due to the fact that the infarctions were larger in the human than in the rabbit material. Also the caliber of the newly formed vessels was greater in the human than in the rabbit hearts.

The newly formed vessels had similar courses in the rabbit and human hearts. They ran circularly, largely parallel with the endocardial surface in both species. The courses of the new vessels formed right angles with those of the normal ones. The abnormal course of the newly formed vessels does not seem to have been commented upon previously in the literature and it is difficult to observe in histologic sections. The course of the newly formed vessels may have practical consequences. The new vessels are probably compressed at each heart contraction when the pressure in the lumen increases. In contrast, the normal vessels are fairly unaffected or perhaps dilated by the myocardial contractions. The circulation in the newly formed vessels can therefore be expected to be poor and to a large extent dependent on the blood pressure. After about 6 weeks there was a regression of the newly formed vessels, so that the old infarction was less vascularized.

Summary

The vascular reaction in cases of experimental myocardial infarction in the rabbit and of myocardial infarction in man has been studied by microangiography. During the first 10 days an irregular and incomplete filling with x-ray contrast medium and dispersed extravasations were obtained in the infarcted areas. After 4 days an ingrowth of newly formed vessels was started. The vessels reached the center of the infarction after about 10 days in the rabbit and somewhat later in the large human infarctions. The new vessels, which were maximally developed after 2 to 4 weeks, had a characteristic course, generally forming right angles with the normal vasculature, that may impair the circulation in them.

REFERENCES

1. Moberg, A. Anastomoses between extracardiac vessels and coronary arteries, Acta Med. Scand. (Suppl.) 149:1, 1964.
2. Fine, G., Morales, A., and Scerpella, J. R. Experimental myocardial infarction, Arch. Path. 82:4, 1966.
3. Hassler, O. Angioarchitecture in hydrocephalus. An autopsy and experimental study with the aid of microangiography. Acta Neuropath. 4:65, 1964.
4. Mallory, G. K., White, P. D., and Salcedo-Salgar, J. The speed of healing of myocardial infarction. A study of the pathologic anatomy in seventy-two cases, Amer. Heart J. 18:647, 1939.
5. Tennant, R., Grayzel, D. M., Sutherland, F. H., and Stringer, S. W. Studies of experimental coronary occlusion, chemical and anatomical changes on the myocardium after coronary ligation, Amer. Heart J. 12:168, 1936.
6. Kaufman, N., Gavan, T. L., and Hill, R. W.: Experimental myocardial infarction in the rat, Arch. Path. 67:482, 1959.
7. Goerttler, K. Die funktionelle Bedeutung des Baues der Gefässwand, Deutsch. Z. Nervenheilk. 170:433, 1953.

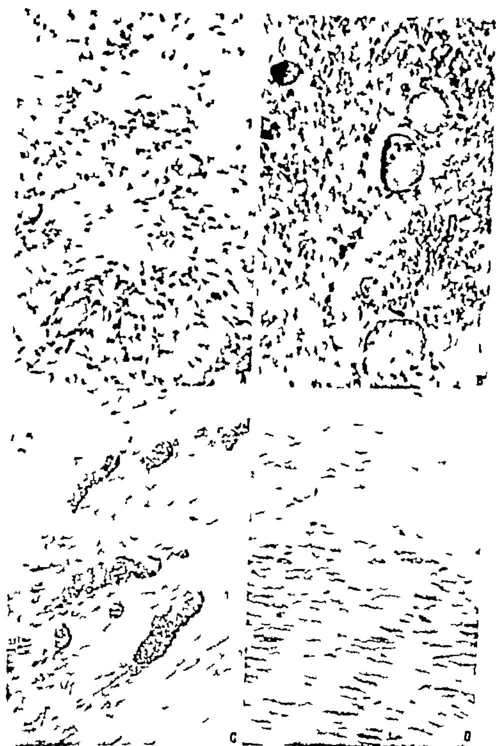


Fig 4 Histological sections through th[illegible] icroangiographed areas of (A) Fig 1 B (B) Fig 1 C (C) Fig 2 C and (D) Fig 3 B (A B [illegible]nd D × 175 C × 75)

Discussion

The present experimental infarctions in the rabbit resembled histologically those obtained by previous authors[3,4,6] and those in human subjects. The difference between the infarctions in the rabbit and those in the human subjects seemed to a great extent to be size. The infarctions in the rabbit hearts were small not only owing to the small size of the rabbit heart but also apparently to the fact that a smaller portion of the total area of supply of the descending branch of the left coronary artery was involved than is usually the case when the descending branch in human hearts is occluded proximally The small amounts of granulation tissue formed in connection with the slight p[illegible]-itis fol

Table I. Pathologic lesions

X-ray dose	Monkey No.	Atrium	Atrial septum	Right ventricle	Left ventricle	Ventricular septum	Myocardial micro-vasculature	Pericardium	Aorta
6,000 Roentgens	1			++++	++	+++	+	++	
	2			+	++		+	+	
	3		+	+	++			++	
	4	++	++++	++++	++++		++	++	
20,000 Roentgens	5	+			+			+	+
	6	++++	++	++++	+++	++	+++	+++	++

The distribution of damage is shown for each animal as well as an estimate of severity from no involvement (blank) to severe (++++).

heart mass. Exposure time took between 10 and 30 minutes. The animals were kept warm during this time and in the subsequent recovery period by external covers. Electrocardiograms were taken immediately after x radiation and at intervals thereafter until the termination of the experiment at five months.

Tissue from the hearts of all animals was removed at the time of death fixed in formaldehyde, and examined histologically after staining with hematoxylin phloxine, and safranine.

Results

Pathologic changes attributable to irradiation were seen in all monkeys with the distribution shown in Table I. All had pericarditis by the time of induced death at five months and four of the six showed grossly thickened, fibrous pericardia. Three monkeys showed increased pericardial vascularity with scattered perivascular accumulations of chronic inflammatory cells.

Major myocardial fibrotic infarctive scars were present in three hearts. Two received 6,000 r and one received 20 000 r. Lesser involvement was seen in the other animal receiving 20 000 r. In this case damage was primarily in the ascending aorta and pericardium. Myocardial lesions were usually full thickness involving total or just subtotal destruction of the myocardium and showed varying stages of progression from hemorrhagic necrosis to hyaline degeneration fatty infiltration and replacement (Figs. 1, 2, and 3). When



Fig. 1. Anterior surface monkey heart 5 months after 20,000 r with extensive full wall fibrosis of right ventricle and right atrium. Original magnification ×1.7

muscle cells survived they tended to be just beneath either the endocardial or epicardial surface (Fig. 2). The intervening muscle mass appeared to have undergone two major changes a marked increase in interstitial connective tissue and direct degenerative muscle changes. These last consisted of ...

Pathologic sequelae of acute cardiac irradiation in monkeys

*Steven J Phillips M D **
*Daniel L Macken M.D ***
*Roberts Rugh Ph D ****
New York N Y

The present study on *Macaca mulatta* is prompted by the increased concern with overt and latent cardiac morbidity from thoracic orthovoltage and super voltage radiation treatment It also includes a review of mammalian cardiac radiation sensitivity An earlier report[1] dealt with acute and short term effects of radiation on the canine heart. The present study deals with changes observed in six adult female rhesus monkeys subjected to precordial x irradiation and sacrificed 5 months later General reviews of different aspects of myocardial sensitivity to irradiation are found in several reports.[2-7]

Materials and methods

The monkeys used were all adult females that had delivered fetuses in captivity All were in good health tuberculin negative on skin test, and maintained on a supranormal diet Five of the six animals had previously received low levels of x irradiation coned to the uterus in early pregnancy but had shown no sequelae to this or subsequent cardiac abnormalities

Prior to cardiac irradiation all animals had standard limb and precordial lead electrocardiograms (ECG s) taken in a carefully maintained supine position under sodium pentobarbital anesthesia (0 5 c.c. per kilogram of body weight intraperitoneally) Heart radiation was then given with the anesthetized animal in a prone position with the dependent precordial region placed over and against a 1 0 cm cone radiation source operating upward and aimed at the mid region of the heart. This provided the closest possible physical relationship between the heart and the x ray source

Four animals received an estimated 6 000 r to the heart and two were given 20 000 r in a single precordial exposure

The x ray source was operated at 184 kv 30 Ma with a HVL of 0 6 mm Cu with filtration of 0 28 mm Cu and 0.50 mm Al Source to the mid-cardiac region varied between 17 and 20 cm dependent on animal size and exposure was given at the rate of 570 r per minute. All dosage was estimated at the mid region of the

From the Radiological Research Laboratory Department of Radiology Columbia University College of Physicians & Surgeons, New York, N Y
Supported by Contract AT(30-1) 2740 from the United States Atomic Energy Commission.
Received for publication June 23 1970
Reprint requests to Dr Robert Rugh, Radiological Research Laboratory 630 West 168 St., New York, N Y 10032.
*Associate Professor of Anatomy Temple University School of Medicine.
**Instructor in Medicine (Cardiology), Columbia University College of Physicians & Surgeons. Present address, Walter Reed Army Institute of Research, Washington, D. C.
***Associate Professor of Radiology (Biology), Columbia University College of Physicians & Surgeons.



Fig 4 Nonspecific monkey myocarditis seen in right ventricle of heart receiving 6,000 Hematoxylin, phloxine, and safranine Original magnification ×560

the small diameter of the x-ray beam and variations in the actual area of irradiation These differences, and the absence of major lesions in two animals receiving 6,000 may also reflect latency of damage expression This may involve protracted periods of time, measured in years, before the injury shows itself objectively In one case, both the anterior and posterior surfaces of the right ventricle showed extensive patchy scarring after 6 000 A second case with 6,000 r had destruction of most of the right atrium and interatrial septum the anterior right and left ventricles, and about two thirds of the interventricular septum (Fig 6) The remaining case of major myocardial damage involved destruction of large portions of the atrial and ventricular walls in the infundibular area in a monkey receiving 20,000 r (Fig 5)

Vascular wall changes were widely seen in the gross myocardial lesions and adjacent areas. They were most prominent in arterioles with outside diameters of 40 to 60 microns. Some showed foam-cell lesions with narrowed or obliterated lumens while other vessels showed total fibrosis (Fig 7) Larger arterial vessels were normal in appearance while some smaller vessels showed exudative perivascular acidophilic accumulations. A number of epicardial veins showed a striking thickening of the medial and adventitial wall with coarse irregularly dense acidophilic connective tissue fibers on the side of the vein adjacent to the myocardium (Fig 8) The epicardial surface of the vein had normally delicate adventitial connective tissue This discontinuous change was seen in all four hearts receiving 6 000 r

Specialized cardiac conduction tissue was significantly involved in two hearts,



Fig 2 Right ventricular wall posterior near interventricular septum 5 months after 6,000 r with lesion involving up to full thickness destruction of myocardium Myocardium replaced by fibrous tissue. Hematoxylin, phloxine and safranine. Original magnification ×16



Fig 3 Anterior right ventricular wall 5 months after 6 000 Subendocardial and myocardial fatty replacement. Hematoxylin phloxine, and safranine Original magnification ×54

type of degeneration in which nuclei tended to persist to late in the process of dissolution though often in altered form or a direct acidophilic hyalinization of muscle fibers with early destruction and loss of nuclei Both forms of degenerative changes were remarkable in the paucity of reactive cellular elements present Large areas of muscle loss were practically acellular Peripherally in some areas giant foreign body cells were seen as well as active histiocytes. Diffuse plasma cell and small round cell infiltrates were more characteristic of regions showing earlier stages of disruption and these areas were accompanied by increased connective tissue. This appearance was quite different from that of normal muscle which contained occasional dense foci of small round cells of the type seen in the nonspecific myocarditis described in monkeys.[8] (Fig 4)

The areas of the heart most extensively damaged were variably located and involved as shown in Table I in part to



Fig. 6 Anterior left ventricular wall, interventricular septum, and right ventricular wall 5 months after 6,000 Hematoxylin, phloxine, and saffranine. Original magnification ×9 75

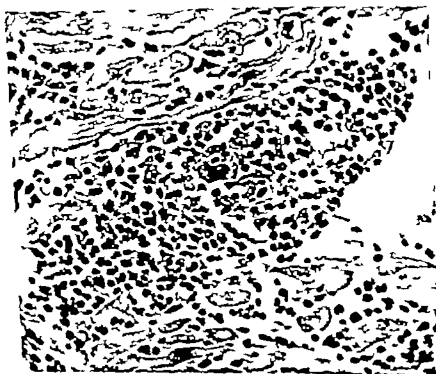


Fig. 7 Fibrotic obliteration of coronary artery and adjacent myocardium in infundibular area of right ventricle 3 months after ?0 000 Hematoxylin, phloxine, and safranine. Original magnification ×470.

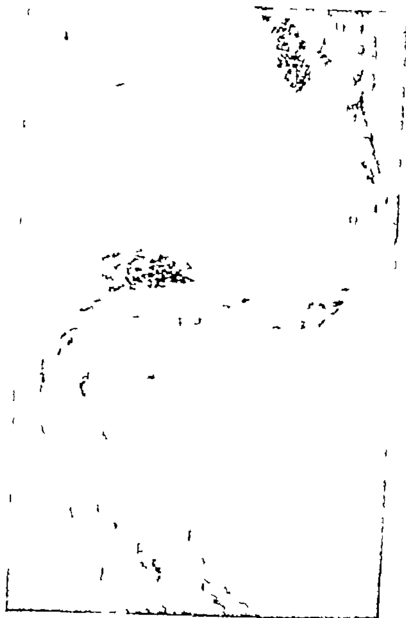


Fig 5 Right atrium near S-A node 5 months after 20 000 r Same heart as Fig 1 Note almost total fibrosis and/or hyaline degeneration of trial myocard um. Hematoxylin phloxine and safranine. Original magnification ×42

one receiving 6 000 and one 20 000 r The latter had atrial lesions involving portions of myocardium in the sinoatrial (S-A) node region where at least 80 per cent of the atrial myocardial fibers were destroyed (Fig 5) The heart rate in this monkey was 55 and no P waves were present in the ECG The former animal that received 6 000 r had extensive fibrotic replacement and scarring in the low interatrial septum and atrioventricular (A V) node region as well as scattered diffuse plasma and round cell infiltration Massive ventricular septal necrosis surrounded conduction tissue and in the region of the common bundle and its left branch there were degenerative changes in scattered conduction fiber fascicles (Fig 9) Cardiographically this monkey showed prolongation of A V conduction and P wave changes. Other ECG changes were minimal and will be reported separately

Vacuolar changes and atheromatous luminal occlusions in adventitial blood vessels as well as atheromatous changes in the lining of the ascending aorta were seen in one monkey This animal also had an area in the ascending aorta showing medial cystic necrosis (Fig 10) Another animal developed in addition a major periaortic accumulation of degenerating fat with crystalline-gritty material ac



Fig. 10 Portion of proximal ascending aorta showing medial cystic necrosis and an atheromatous plaque 5 months after 6 000 Hematoxylin, phloxine, and safranine. Original magnification ×55.

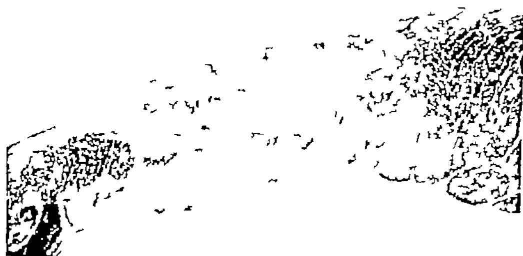


Fig. 11 Anterior right ventricular all 5 months after 20 000 showing gross damage to infundibular region. Hematoxylin, phloxine, and safranine. Original magnification ×25

cumulated in its margins. These areas showed patchy inclusions of crystalline material suggesting calcium deposition when examined with a polarizing microscope.

Discussion

The cardiac lesions seen in monkeys and dogs several months after acute irradiation differ significantly from the purely obstructive type of lesion produced by microspheres or by coronary ligation[14] in that the process has a protracted latency in its appearance. Plasma cells, giant cells, and basophilic histiocytes are still very much in evidence at least as long as 5 months after the initial acute injury. However they all share in a common tendency to a subendocardial sparing of tissue. This is in contrast to the subendocardial necrosis hemorrhage and zonal lesions reported after hemorrhagic shock.[11] The changes seen are not qualitatively any different from those summarized by Warren[7] as



Fig 8 Epicardial vein showing dense thickening of wall adjacent to myocardium 5 months after 6,000 r Hematoxylin phloxine and safranine Original magnification ×560



Fig 9 Portion of left bundle branch with damaged conduction tissue in upper interventricular septum 5 months after 6 000 r Hematoxylin phloxine, and safranine. Original magnification ×270.

points on chronic radiation exposure from radium for comparison with acute and more conventionally given fractionated x-ray dosage. In this case, a 44-year-old female patient with a breast malignancy was treated with multiple radium needles. One of these, containing 2 mg of radium sulphate, became dislodged and embedded secondarily in the lower portion of the interventricular septum. Its position was stable by x ray for 3 years until the patient's death. At post mortem a major part of the adjacent septum was totally destroyed. The free left ventricular wall appeared histologically normal In calculating the delivered dosage and geometry [4] it was seen that the immediately adjacent area received a million roentgens in this 3 year period At 1 9 cm from the needle, the edge of the zone of total necrosis and fibrosis, the accumulated dosage stands at 60,000 r at 3 8 cm. the dosage is calculated at 25 600 r It is this region which marks the edge of the zone of partial muscle necrosis, which is strikingly similar in microscopic appearance to the destruction seen here in the monkey and that seen in the dog heart with acute irradiation The remainder of the patient's heart is calculated to have received at least 9 000 r in the three years. However histological examination of sections of the wall of the left ventricle revealed normal myocardium.

If we consider for the moment the differences between a radium source and an x-ray beam source relevant to the differences in source volume and tissue recuperative response, then we may say that the 25 600 r figure is comparable in its effect, as measured by the gross lesions produced with that produced by 5,000 to 7 000 r given acutely to the monkey or dog heart in our experience Doses of 5 000 to 7 000 r have all produced infarctive damage in the myocardium as seen with the electrocardiogram grossly and histologically Some acute dosage less than 3 000 r will produce no major damage. This figure appears to be between 2,000 and 3 000 r but is not well fixed.

In between these figures for acute and chronic irradiation effects lies the field of practical radiotherapeutic usage of fractionated dosage that is at rates in the range of 500 r to 1 000 r per week with total tissue doses of 5 000 to 6,000 r Dosage in this range has been generally believed to be without any major myocardial deleterious effect.[4,14-16] Some doses larger than 5 000 r given under similar protracted conditions, presumably would produce major damage to the heart. The risk of radical irradiation therapy is a calculated risk only if the normal tissue sensitivities are known. In the case of the heart they are not known and the present experiments and review are in part concerned with this question.

Since radiation effects on biological tissues tend to be incremental and reproducible, the ratio of dose not producing injury to that producing major injury can be compared under the above conditions with ratios suggested by chronic and acute heart irradiation experiences. On this basis, if 5,000 r given in fractionated doses over 5 weeks is innocuous to the heart, then this calculation suggests that some dose between 8,350 r and 14 400 r will be critically destructive to the heart. Such dose is more likely to be nearer the lower one These figures are derived from comparing the ratios present in acute and chronic irradiation situations with those in the fractionated dosage situation The estimate lacks precision only insofar as the acute and chronic figures themselves are imprecise.

This type of analysis does, however help in evaluating published usage figures. Abbott[21] treated 32 patients with 2,200 r in 3 days time prior to pneumonectomy without any cardiac complications. Mark and co-workers[22] gave a series of patients 6,000 r over 6 weeks and was aware of a distinctly higher incidence of cardiac complications in contrast to his control group of patients receiving no irradiation prior to pneumonectomy In the first case, the dosage approaches the acute form and is in the nondestructive range, whereas the 6 000 r fractionated dosage more clearly approaches the harmful range. Similarly Pierquin and associates[23] reported on six patients with esophageal lesions who had received between 6,000 and 6 900 r Three of these had degenerative cardiac lesions one with an abnormal ECG However In



Fig 12 Posterior right ventricular wall 5 months after 6 000 r Detail of fibrosis and myolysis shown in Fig 1 Hematoxylin phloxine, and safranine Original magnification ×270.

general products of x irradiation aseptic necrosis hyaline fibrosis and obliterative vascular change

In man acute exposure to cardiac destructive amounts of irradiation has been very limited The hearts of 76 Japanese people who died within 7 to 42 days of whole body massive exposure at the close of World War II showed perivascular edema interstitial or subendocardial hemorrhage and subepicardial foci of plasma cells.[13] Particularly in individuals with short survival focal necrosis of the myocardium was present In one individual hemorrhage was seen on the common bundle high in the interventricular septum

Of the reported radiation accidents that have occurred since the nuclear excursion described by Karas and Stanbury[13] in which a 38-year-old man received 8 800 rad is of most interest. The principal clinical problem in the care of this patient was maintenance of the blood pressure and the competence of the heart. Autopsy disclosed hydropericardium acute pericarditis interstitial myocarditis and periaortitis of the ascending aorta Kundel[1] too has called attention to cardiovascular effects in the acute radiation syndrome. He found in monkeys receiving 3 900 and 6 600 rad whole body irradiation that cardiac output fell substantially in the first 18 hours. He felt however that the changes were mainly due to peripheral vascular effects.

The fundamental questions are What is the radiation sensitivity of the heart and how is it dependent on different conditions of exposure? To answer this a diverse body of information is available since the heart and blood vessels have been irradiated under variable conditions for well over 60 years.

In an attempt to unify this information our attention has focused on the report of Ross[14] in 1932 which provides some fixed

points on chronic radiation exposure from radium for comparison with acute and more conventionally given fractionated x-ray dosage. In this case a 44 year-old female patient with a breast malignancy was treated with multiple radium needles. One of these containing mg of radium sulphate, became dislodged and embedded secondarily in the lower portion of the interventricular septum. Its position was stable by x-ray for 3 years until the patient's death. At post mortem a major part of the adjacent septum was totally destroyed. The free left ventricular wall appeared histologically normal. In calculating the delivered dosage and geometry[4] it was seen that the immediately adjacent area received a million roentgens in this 3 year period. At 1.9 cm from the needle, the edge of the zone of total necrosis and fibrosis, the accumulated dosage stands at 80,000 r; at 3.8 cm, the dosage is calculated at 25,600 r. It is this region which marks the edge of the zone of partial muscle necrosis, which is strikingly similar in microscopic appearance to the destruction seen here in the monkey and that seen in the dog heart with acute irradiation. The remainder of the patient's heart is calculated to have received at least 9,000 r in the three years. However histological examination of sections of the wall of the left ventricle revealed normal myocardium.

If we consider for the moment the differences between a radium source and an x-ray beam source relevant to the differences in source volume and tissue recuperative response, then we may say that the 25,600 figure is comparable in its effect as measured by the gross lesions produced with that produced by 5,000 to 7,000 r given acutely to the monkey or dog heart in our experience. Doses of 5,000 to 7,000 r have all produced infarctive damage in the myocardium as seen with the electrocardiogram grossly and histologically. Some acute dosage less than 5,000 r will produce no major damage. This figure appears to be between 2,000 and 3,000 r but is not well fixed.

In between these figures for acute and chronic irradiation effects lies the field of practical radiotherapeutic usage of fractionated dosage, that is at rates in the range of 500 r to 1,000 r per week with total tissue doses of 3,000 to 6,000 r. Dosage in this range has been generally believed to be without any major myocardial deleterious effect.[14, 9] Some doses larger than 5,000 r given under similar protracted conditions, presumably would produce major damage to the heart. The risk of radical irradiation therapy is a calculated risk only if the normal tissue sensitivities are known.[3] In the case of the heart they are not known and the present experiments and review are in part concerned with this question.

Since radiation effects on biological tissues tend to be incremental and reproducible, the ratio of dose not producing injury to that producing major injury can be compared under the above conditions with ratios suggested by chronic and acute heart irradiation experiences. On this basis, if 5,000 r given in fractionated doses over 5 weeks is innocuous to the heart, then this calculation suggests that some dose between 8,330 r and 14,400 r will be critically destructive to the heart. Such dose is more likely to be nearer the lower one. These figures are derived from comparing the ratios present in acute and chronic irradiation situations with those in the fractionated dosage situation. The estimate lacks precision only insofar as the acute and chronic figures themselves are imprecise.

This type of analysis does, however, help in evaluating published usage figures. Abbott[22] treated 32 patients with 2,200 r in 3 days' time prior to pneumonectomy without any cardiac complications. Mark and co-workers[23] gave a series of patients 6,000 r over 6 weeks and was aware of a distinctly higher incidence of cardiac complications in contrast to his control group of patients receiving no irradiation prior to pneumonectomy. In the first case the dosage approaches the acute form and is in the nondestructive range, whereas the 6,000 r fractionated dosage more clearly approaches the harmful range. Similarly Pierquin and associates[24] reported on six patients with esophageal lesions who had received between 6,000 and 6,900 r. Three of these had degenerative cardiac lesions, one with an abnormal ECG. However in



Fig. 12 Posterior right ventricular wall 5 months after 6 000 r Detail of fibrosis and myolysis shown in Fig. 2. Hematoxylin phloxine, and saframine Orig nal magnification ×270.

general products of x irradiation aseptic necrosis hyaline fibrosis and obliterative vascular change

In man acute exposure to cardiac destructive amounts of irradiation has been very limited The hearts of 76 Japanese people who died within 7 to 42 days of whole body massive exposure at the close of World War II showed perivascular edema interstitial or subendocardial hemorrhage and subepicardial foci of plasma cells[13] Particularly in individuals with short survival focal necrosis of the myocardium was present. In one individual hemorrhage was seen on the common bundle high in the interventricular septum

Of the reported radiation accidents that have occurred since the nuclear excursion described by Karas and Stanbury[13] in which a 38 year-old man received 8 800 rad is of most interest. The principal clinical problem in the care of this patient was maintenance of the blood pressure and the competence of the heart. Autopsy disclosed hydropericardium acute pericarditis interstitial myocarditis and periaortitis of the ascending aorta. Kundel[14] too has called attention to cardiovascular effects in the acute radiation syndrome. He found in monkeys receiving 3 900 and 6 600 rad whole body irradiation that cardiac output fell substantially in the first 18 hours He felt however that the changes were mainly due to peripheral vascular effects.

The fundamental questions are What is the radiation sensitivity of the heart and how is it dependent on different conditions of exposure? To answer this a diverse body of information is available, since the heart and blood vessels have been irradiated under variable conditions for well over 60 years.

In an attempt to unify this information our attention has focused on the report of Ross[15] in 1932 which provides some fixed

cent. Kirkpatrick using rabbit ear arteries, found that if they were hyperlipemic, any dose from 500 to 4 000 r given acutely or in 2 or 3 days produced *foam-cell* lesions of the artery with a latency of 16 to 18 days and a maximal development at 9 weeks. Lead-shielded portions of the same artery were free of lesions as long as 20 months later. In normolipemic rabbits similar irradiation produced only a few small fibrous plaques and no foam-cell lesions after 9 weeks. Parallel to this is the report[39] of a 27 year-old man with a mediastinal metastatic testicular malignancy who received 1 650 r precordially, developed cardiac and pulmonary failure and died. Autopsy *revealed advanced* pulmonary artery and aortic atherosclerosis, extensive myocardial fibrosis, and irregular thickening of both coronary arteries and veins. Stewart and co-workers case[4] of a 15-year-old boy who died of a myocardial infarction 16 months after 4 000 rad to 50 per cent of the heart is of particular interest. There was no metabolic or familial predisposition to atherosclerosis, yet autopsy showed intimal proliferation and atheromatous deposition in the coronary arteries along with a fresh myocardial infarction. Prentice[40] described a 19-year-old boy with an acute myocardial infarction who received a thoracic dosage of 3,250 r four years earlier for Hodgkins disease. At autopsy his coronary arteries showed extensive atheromatous changes and a large infarct of the left ventricle and septum was present. Blood vessels elsewhere showed no atheromatous changes.

Results which do not readily fit into the projected radiation response range are those of Rubin and associates[41] where 6,000 to 10 000 *r given rotationally* produced no significant ECG or tissue changes in four patients who came to autopsy. Another divergent report[42] cites two patients who received 2,360 and 2 920 rad and who subsequently had major cardiac lesions. The first had cardiac fibrosis, pericarditis, and hyalinized thickened arteries, while the second patient had a full thickness lesion of the outflow tract of the right ventricle.

In marked contrast with our experience, Moss and associates,[43] using a 1,000 KVP source gave 5,000 and 10 000 r percordially to dogs without any effect as seen at death at 106 and 69 days, respectively while dogs given 20 000 r had major destructive lesions of the myocardium after a 10 day latency period.

The often quoted papers of Leach and Sugiura[44,45] in which 7,500 r acutely had no effect and 10 000 r was destructive to the heart of rats, makes more sense if the delivered dosage is figured for the mid region of the heart using penetration percentages furnished in the original article. Under these circumstances the dosage producing lesions is 8 000 r and that yielding *no appreciable* damage is 6 000 r.

Another series of papers difficult to interpret is the joint work of Bishop and associates[47] and Stone and co-workers[48,49] who used a ^{60}Co unit with a 4 cm. x 4 cm port position over the right or left aspect of the heart of dogs. They found that a right sided dose of as little as 4,800 r produced limited right ventricular and total atrial fibrosis. Giving 9 600 r from the right side produced right ventricular failure death and damage to 70 to 100 per cent of the right ventricle and patchy portions of the interventricular septum. With this exposure, the left ventricle received an estimated 8,200 r yet there was no clinical or pathological change up to 36 days after *irradiation. They described* a similar beam directed from the left side to give 8 400 r to the left ventricle. Left ventricular failure, death and damage to 40 to 70 per cent of the left ventricle was observed. There was no damage to the interventricular septum or right ventricle which had received an estimated 7,200 r. It is difficult to understand how with a dosage from one direction to the left ventricle (8 200 r and a 36 day survival) no injury is seen while with a second angle of incidence and a calculated dose of 8 400 r with a survival *time* of 40 days, between 40 and 70 per cent of the left ventricle is grossly damaged.

Supplementary chromosomes[50] may serve a role in the relative resistance of the *myo*cardium to irradiation compared to other tissues. Many myocardial cells are binucleate and some multinucleate. In addition,

this and many other clinical reports which mention cardiac complication there is some doubt as to whether the cardiac condition or disease state predated the radiation and is merely a coincidence because of the involved age group For this reason information establishing the correct sensitivities for the heart should be sought in a young patient population or in healthy experimental animals with response patterns similar to man

A difficult aspect of comparing the results in the literature is the wide range of cardiac involvement reported e g from transient T wave changes to verified pericarditis[21-23] and frank infarction [24] As was noted in one recent review[3] and certainly in our experience the right side of the heart tends to be more severely damaged than the left. This difference may be on the basis of its more superficial location Similarly the pericardium is especially prone to radiation damage as we also have seen in both monkey and dog Stewart and co-workers[6] recently reported that 3 4 per cent of patients treated for breast malignancy and 5 8 per cent of those treated for thoracic lymphoma who survived at least one year showed heart disease primarily pericardial with a latency varying from 5 months to 4 years. In 25 of those with cardiac manifestations 22 received doses over 4 000 r Twenty three had pericarditis. Ten of these developed constrictive pericarditis. Included in this group were a young patient with myocardial infarction and coronary artery disease four years after 4 000 rad who is discussed below and one young patient with myocardial fibrosis leading to mitral insufficiency and a left bundle branch block who received 4 700 rad eight years earlier They felt that the photon energy of the radiation was not as important as the total dosage in determining an approximate 4 000 rad threshold for damage to normal heart structures, in this case primarily pericardial complications Steinberg[27] reports two cases of effusive-constrictive pericarditis one 20 years after radiation and one occurring two years after 6 000 rad Similar complications after 4 800 r[28] and 8,250 r[29] have been reported

The idiosyncracies of a particular experimental animal cannot be ignored Soto and associates[8] documented the presence of a primary myocarditis in rhesus monkeys of completely unknown etiology and which lacked ECG evidence of its presence in 18 of 20 examined monkeys. Malmos[30] also pointed out as has been our experience that this diffuse focal myocarditis is common in monkeys. He had not seen however scarring in untreated animals occurring to the extent we report. Gedigk and Giersberg[31] describe fat replacement of scar tissue in the heart as rare and usually secondary to coronary artery changes. In our monkeys however large blood vessels appear to be intact although many of the smaller vessels are scarred (Fig 8) This lesion also does not fit that seen in congenital aplasia of the right ventricle[32-34] where the endocardium is markedly thickened In view of the other extensive pathology in this heart this lesion seems more likely a portion of the radiation damage.

Age is also a factor in cardiac radiation sensitivity Copenhaver and co-workers[35] found that in early development of the heart in Amblystoma retardation of cardiac development was proportional to the radiation dose and inversely proportional to the stage of differentiation Even in this early stage the heart has an 8 to 12 day latency in showing the effect of the irradiation At early stages, 250 r will produce heart anomalies at later stages, 500 r is required for a similar effect. In spite of the increased fetal sensitivity to irradiation some doses are without apparent effect on the heart Coppenger and Brown[36] gave rats in utero from day 1 through 21 50 r per day and found their hearts were completely normal in development and weight up to one year later

Rabbits have a very low threshold to radiation induced cardiovascular lesions especially if they are made hyperlipemic by cholesterol feeding [7] This led to the suggestion that the patient with already damaged coronary vessels would experience an acceleration of this process secondary to irradiation. However Vinke [37] in his 10 patients receiving 6 000 r for esophageal lesion had no ECG changes in 3 to 13 months even though the patients had serum cholesterols over 260 mg per

. conjunction with the cited studies
rongly suggests that precordial thera
eutic irradiation at or only slightly
eyond currently used dosage is a po-
ential cause of extensive cardiac mor
idity

The authors wish to express their appreciation to Dr Alan D Conger for his interest and comments on this study

REFERENCES

1. Phillips, S. J Reid, J A., and Rugh, R. Electrocardiographic and pathologic changes after cardiac x-irradiation in dogs, AMER. HEART J 68:524, 1964.
2. deBoer W G. R. M Experimentele en therapeutische Roentgenbestraling als oorzaak van arteriele en cardiale beschadiging, Doctoral dissertation, Groningen, 1963
3. Ferri, G. G and Dusi, U Radiazioni ionizzanti e cuore. I Rassegna della letteratura recente, Quaderni di radiologia 30 1007 1965.
4. Jones, A., and Wedgwood, J Effects of radiations on the heart, Brit. J Radiol. 33 138, 1960.
5. Smith, D J The cardiovascular effects of ionizing radiations. A tribute to Arthur Ulderie Desjardins, M.D J Maine Med. Ass. 49:205 1958.
6. Stewart, J R Cohn, K. E F Jardo, L F., Hancock, E. W and Kaplan, H. S Radiation-induced heart disease. A study of twenty-five patients, Radiology 89:302, 1967
7. Warren, S. Effects of radiation on normal tissues. VI Effects of radiation on the cardiovascular system, Arch. Path. 34 10 0, 1942.
8. Soto, P J J Beall, F A Nakamura, R. M and Kupferber L. L Myocarditis in rhesus monkeys, Arch. Path. 78:681 1964.
9. Bing, R. J Castellanos, A., Bradel, E Lupton, C., and Siegel, A. Experimental myocardial infarction. Circulatory biochemical and pathologic changes, Amer J Med Sci 232:533 1956.
10. Strehler B. L., Wider R., Raychaudhuri, A Gee, M and Press, G. Studies on the mechanism of cellular death. III Changes in proteins and connective tissue elements during early and late cardiac necrosis, J Geront. 22:520, 1967
11. Martin, A. M J and Hackel, D B An electron microscopic study of the progression of myocardial lesions in the dog after hemorrhagic shock, Lab Invest. 15:243, 1966.
12. Liebow A. A Warren, S and DeCoursey E. Pathology of atomic bomb casualties, Amer J Path. 25:853, 1949
13. Karas, J S. and Stanbury J B F tal radiation syndrome from an accidental nuclear excursion, NEJM 272 755 1965.
14. Kundel, H. L. The effect of gamma irradiation on the cardiovascular system of the rhesus monkey Radiat. Res. 27 406, 1966.
15. Ross, J M.: A case illustrating the effects of prolonged action of radium, J P th. Bact. 35:899 1932.
16. Bloom, H. J G. Discussion on the changes produced in tissues by irradiation, Proc. Roy Soc. Med. 52 193 1959
17. Catterall M and Evans, W: Myocardial injury from therapeutic irradiation, Brit. Heart J 22:168, 1960.
18. Ellinger F Medical radiation biology Springfield Ill., 1957 Charles C Thomas, Publisher
19. Vaeth, J M., Feigenbaum, L. A., nd Merrill, M. D: Effects of intensive radiation on the human heart, Radiology 6 755 1961
20. Friedman, M.: Concepts of radical irradiation therapy C. A. Bull. Cancer Progress 3:20, 1953.
21. Abbott, O Discussion of paper by Mark et al. J Thorac. Cardiovasc. Surg. 51:34, 1966.
22. Mark, J B. D Call, E. P and von Essen, C. F: Preoperative irradiation in patients undergoing pneumonectomy for carcinoma of the lung, J Thorac. Cardiovasc. Surg. 51:30, 1966.
23. Pierquin, B Tubiana, M and Dutreix, J Etude de 54 cas de cancers de l'oesophage thoracique traites par le betatron (22 M V) J Radiol. Electr 39:725 1958.
24. Macleod, D S., Roth, C. T Jr and Harris, J H.: Postradiation pericarditis with chronic pericardial effusion, Ann. Intern. Med. 69:07 1968.
25. M rgin, F M., and Casselleth, P A. Constrictive pericarditis following radiation therapy Amer J Med. 44 116, 1968.
26. Dollinger M R., Lavine, D M and Foye, L. V J Myocardial infarction due to post irradiation fibrosis of the coronary arteries, J.A.M.A. 195:316, 1966.
27. Steinberg, I., Effusive-constrictive radiation pericarditis. T cases illustrating value of ngiocardiography in diagnosis, Amer J Cardiol. 19:434, 1967
28. Hurst, D W Radiation fibrosis of pericardium, with cardiac tamponade, Canad. M.A J 81 377 1959
29. Blumenfeld, H and Thomas, S. F Chronic massive pericardial effusion following roentgen therapy for carcinoma of the breast, Radiology 44:335, 1945.
30. Malinow M R. Personal communication, 1965.
31. Gedigk, P and Giersberg, O. Uber die Entstehung von Fettgewebe in Herzmuskelschwielen, Virchows Arch. Path. Anat. 339:275 1965.
32. Cumming, G. R., Bowman, J M. M., and Whytehead, L. Congenital aplasia of the myocardium of the right ventricle (Uhl's anomaly) AMER. HEART J 70:671 1965.
33. Perrin, E. V and Mehrizi, A. Isolated free-wall hypoplasia of the right ventricle, Amer J Dis. Child. 109:558, 1965.
34. Gould, L., Guttman, B., Carrasco, J and Lyon, A. F.: Partial absence of the right ventricular musculature, Amer J Med. 43:632, 1967
35. Copenhaver W M., van Dyke, R. H., and Rugh, R.: Effects of x-irradiation on embryos

Kompmann and associates[41] have found that human heart nuclei are highly poly ploid i e as many as 80 per cent of the muscle nuclei have more than the diploid amount of chromosomal material Because of the nondividing nature of myocardial cells the usual lethal effects of radiation on dividing cells are not seen More slowly expressed actions involving macromolecu lar synthesis might well occur with a long latent period being involved[42] In the case of the heart reacting to stress with hyper trophy as many as 60 per cent of the cell nuclei may be octaploid in character[41] That this type of injury may be occult as seen in conventional histology is well demonstrated by the work of Wellmann and co-workers[43] and Volk and associ ates[44] where with the exteriorized canine pancreas subjected to 5 000 to 9 000 r they found a permanent depression in pancreatic enzyme output even one year later though to all appearances the cells had recovered all their fine detail Kosnider and co-workers[45] found that, in rabbit hearts given 200 to 1 000 r acutely there was a distinct reduction in DNA as seen in Feulgen preparations. Similar losses in DNA in the heart in rats have been measured after 700 r acute whole body irradiation[46] In addition in mice and rabbits subjected to radiomimetic zone treatment, cardiac muscle nuclei undergo dissolution similar to that seen in radia tion[47]

Under the influence of irradiation there is considerable evidence that the cardiac muscle cell becomes more permeable DeBoer[4] showed that this was part of the acute response to radiation in hyperlipemic rabbits when he demonstrated the diffuse uptake of tetracycline after a single dose of 2 000 r Bekhor and co-workers[48] also found an increased permeability of the rat heart muscle cell to the nonmetabolite α aminoisobutyric acid after a dose of 600 r Apparently myocardial catechol amine stores are not dynamically involved in the radiation reaction since acute doses to the heart in the rat of up to 40 000 r caused no change in the myocardial con tent, while a dose of 7 200 r followed for a period up to 43 days showed no change in the heart s store.[49] In addition Sottocasa and associates[50] working with beef heart slices noted it was only with doses in excess of 9 652 r that any significant amount of β-glucuronidase, one of the acid hydrolases found in lysosomes, was released They concluded that this was not a direct effect on the lysosomal mem brane but instead was an action mediated by the intact cell

The above described changes are concomitant with the vascular and connective tissue changes classically reported with irradiation injury The endothelium and basement membrane of blood vessels are particularly affected in addition peri vascular collagen may lose its cross striation[50] McDonald and Hayes[51] have shown in the brain subjected to 2 400 to 6,500 rad there is an appreciable thickening of the capillary basal lamina after one to 3 months latency Edema and an increase in vacuolar endothelial cell inclusions was also observed Basic changes in connective tissue reactivity in the heart after injury persist for long periods of time after the initial injury period[10] Rhoades[52] too felt that the initial vascular changes were due to connective tissue alteration. DeBoer[4] advanced the idea that the primary vascular effect resulting in increased per meability was secondary to a depolymeri zation of mucopolysaccharides in the con nective tissue of the vascular wall. This injury ultimately led to artheromatous changes He also emphasized a primary action of irradiation on the myocardium leading to what Schweitzer[53] earlier had described as myoplasmolysis. Twenty patients with irradiation myocardial in jury but without major vessel alterations were presented as was his demonstration of the increased permeability of irradi ated myocardial cells. These irradiation changes have been corroborated in a recent study[54] showing alterations in the fine structure of myocardial cells seven years after a mediastinal dose of 5 200 rad

Summary

A review of cardiac damage secondary to irradiation is presented as well as in formation on six adult monkeys given acute precordial irradiation and put to death at five months. The data presented

Case reports

Hypertrophic subaortic stenosis complicated by aortic insufficiency and subacute bacterial endocarditis

James U Cardelia M.D
Benjamin Befeler M.D
Frank J Hildner M.D
Philip Samet M.D
Miami Beach Fla.

Idiopathic hypertrophic subaortic stenosis (IHSS) is being recognized with increasing frequency Associated valvular aortic stenosis complicating or dominating the clinical course of illness has been recently stressed, both as to its frequency and prognostic significance. Murmurs of aortic insufficiency occurring in patients with IHSS have been rarely described [4] bacterial endocarditis complicating hyper trophic subaortic stenosis has been recog nized in only a few instances.[1-4] This report describes the unusual association of idiopathic subaortic stenosis with pure aortic insufficiency in a patient with a documented history of subacute bacterial endocarditis (SBE)

Case report

M R 58-year-old Caucasian man, as referred to the Mount Sinai Hospital of Greater Miami in November 1969 for cardiac evaluation. H knew of heart murmur discovered on routine examination t age 20. There was no history of rheumatic fever He as ell until September 1963 when he developed recurring fever night eats, increasing fatigability nd periodic nondescript anterior hest pain, for hich he was hospitalized elsewhere. The diagnosis of ubacute bacterial endocarditis was made following the isolation of *Str ptococcus viridans* from the blood on four separate cultures. He was treated ith mass doses of penicillin dur g 12 eek hospitalization nd as subsequently given daily penicillin prophylaxis. Thereafter he did well until February 1965 hen he was hospitalized because of sudden, severe chest pain, ith clinical and radiographic features of pulmonary infarction. Because of protracted febrile course and previous history of endocarditis, he was again treated for bacterial endocarditis, this time with penicillin and streptomycin for 7 weeks. H had complained of occasional chest pain consistent ith angina pectoris for the past year There as minimal exertional dyspnea, but no orthopnea, paroxysmal nocturnal dyspnea (PND) edema, palpitations, vertigo, or syncope.

Physical examination revealed middle-aged man in no distress. The blood pressure was 100/50 in the right arm, the pulse was 80 per minute, and respirations ere 16 per minute and regular The temperature as normal. There was no evidence of heart failure. The carotid pulses ere brisk ith rapid upstroke. The cardiac pex beat as single, i the fifth intercostal space, just outside the midcla icular line. N rub or gallop was noted. The first heart sound as normal. The second sound in the aortic

From the Section of Cardiology Department of Internal Medicine, Mount Sinai Hospital, Miami Beach, Fla.
Received for publication Feb. 6, 970.
Reprint requests to: James U. Cardelia, M.D Section of Cardiovascular Disease, Department of Internal Medicine, Mount Sinai Hospital of Greater Miami, 4300 Alton Road, Miami Beach, Fla. 33 40.

at critical stages of heart development Yale J Biol Med 32:171 1960

36. Coppenger C J and Brown S O Postnatal manifestations in albino rats continuously irradiated during prenatal development T xa Report Biol Med 23:45 1965
37. Ynke B The incidental effect on the heart of x ray irradiation Acta Med Scand 1 2:711 1962
38. Kirkpatrick J B Pathogenesis of foam cell lesions in irradiated arteries Amer J Path 50:291 1967
39. Lamberts, H B and deBoer W C R M Contribution to the study of immediate and early x ray reactions with regard to chemoprotection IX X ray induced coronary occlusion leading to heart damage in rabbits, Int J Radiat. Biol 8:359 1964
40. Prentice R T W Myocardial infarction following radiation Lancet 2:388 1965.
41. Rubin P Andrews J R Eaton R and Flick A Response of radiation pneumonitis to adrenocorticoids, Amer J Roentgen. 91:153 1958.
42. Rubin E Camara J Grayzel D M and Zak F G Radiation-induced cardiac fibrosis, Amer J Med 31:71 1963
43. Moss A J Smith D W Michaelson S Schreiner B F and Murphy C W Radiation induced acute myocardial infarction in the dog University of Rochester Atomic Energy Project UR-625 Rochester N Y 1963
44. Leach J F and Sugiura K The effect of high voltage roentgen rays on the heart of adult rats, Amer J Roentgen 48:81 1942
45. Leach J E and Sugiura K The effect of high voltage roentgen rays on the heart of adult rats, Amer J Roentgen 45:414 1941
46. Cession-Fossion, A and Beaumariage M L Teneur en catecholamines du myocarde et des glandes surrenales du rat apres irradiation aux rayons X Int J Radiat Biol. 10:277 1965
47. Bishop, V S Stone H L Yates, J Simek J and Davis, J A. Effects of external irradiation of the heart on cardiac output venous pressure and arterial pressure, J Nucl. Med. 6:645 1965
48. Stone, H L Bishop V S and Guyton A C Progressive changes in cardiovascular function after unilateral heart irradiation Amer J Physiol 206:289 1964
49. Stone, H L Bishop V S. and Guyton, A C Ventricular function following radiation damage of the right ventricle Amer J Physiol 211:1 09 1966
50. Puck T T: The action of radiation on mammalian cells, The Amer Naturalist 9:65 1960
51. Kompmann M Paddags, I and Sandritter W: Feulgen cytophotometric DNA determinations on human hearts, Arch. Path. 8:303 1966.
52. Puck T T Cellular aspects of irradiation and aging in mammals, Fed. Proc. 20:31 1961
53. Wellmann, K. F Volk, B. W and Lewitan, A The effect of radiation on the fine structure and enzyme content of the dog pancreas. II. Long term studies, Lab. Invest. 15:1007 1966.
54. Volk, B W Wellmann, K. F and Lewitan, A The effect of irradiation on the fine structure and enzymes of the dog pancreas. I Short-term studies Amer J Pathol 18:7 1 1966.
55. Kozminder S Szczurek Z and Petelenz, T The pathomorphology of the heart muscle in experimental radiation disease in rabbits, Arch. Immun. Ther Exp. 10:116, 1962.
56. Caster W O Armstrong, W D and Simonson, L. Changes in the cardiovascular system following total body x irradiation Amer J Physiol 188:169 1957
57. Brinkman R Lamberts, H B and Veninga, T S Radiomimetic toxicity of ozonized air Lancet 1 133 1964
58. Bekhor I J Shah P Thomas, D W and Bavetta L A The effect of whole-body x irradiation on amino acid transport by lymphatic tissues, Radiat Res. 21:223, 1964.
59. Sottocasa G. L. Glass, G and deBernard, B. The effect of x irradiation on the activities of some lysosomal hydrolases of heart tissue, Radiat Res. 24:32 1965
60. Leroy E P Liebner E J and Jensik, R J The ultrastructure of canine alveoli after supervoltage irradiation of the thorax. I Lesion of the latent period Lab. Invest. 15:1544 1966
61. McDonald L W and Hayes, T W The role of capillaries in the pathogenesis of delayed radionecrosis of brain, Amer J Path 50:745, 1967
62. Rhoades, R P The vascular system in Bloom W ed tor Histopathology of irradiation from external and internal sources, New York 1948, McGraw Hill Book Company Inc.
63. Schweitzer E. Über periphere rontgenschadigungen des herzmuskels, Strahlentherapie 18:812 1924
64. Burch G E Sohal R S Sun S C Miller G C and Colcolough H L. Effect of radiation on the human heart An electron microscopic study Arch Intern. Med 121:230, 1968.



Fig. 3A Illustrates the large intracavitary gradient within the left ventricle as measured simultaneously by the transseptal catheter in the left ventricular inflow tract and the retrograde catheter in the left ventricular outflow tract.



Fig. 3B Shows the position of the catheters used in recording the intracavitary gradient as seen fluoroscopically in the posteroanterior projection.

area was louder than in the pulmonic area. S_2 was not split or accentuated. A Grade 3/6 ejection systolic murmur was heard along the left sternal border not transmitted to the neck. At the lower sternal border another murmur was audible, holosystolic in character which was transmitted to the apex and axilla. An early high-pitched blowing diastolic murmur was present at the upper left sternal border. The remainder of the physical examination was unremarkable.

Routine laboratory investigations were normal. The electrocardiogram revealed left ventricular hypertrophy (Fig. 1). Cardiac fluoroscopy revealed slight left atrial and moderate left ventricular enlargement. The transverse cardiac diameter was moderately increased with markedly increased left ventricular and aortic pulsations. There was no calcification seen in the aortic or mitral valve areas.

Cardiac catheterization was performed on Dec. 1 1969. Right heart pressures were normal and no right-sided gradients were found. No evidence of left-to-right shunt was present by the double-draw indicator-dilution technique. The resting cardiac index was 2.42 L. per minute per square meter

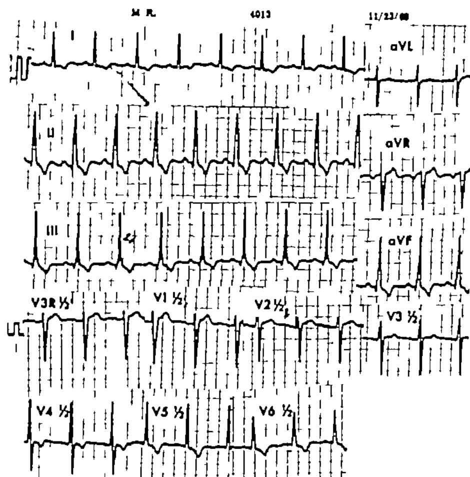


Fig 1 Standard electrocardiogram showing obvious pattern of left ventricular hypertrophy

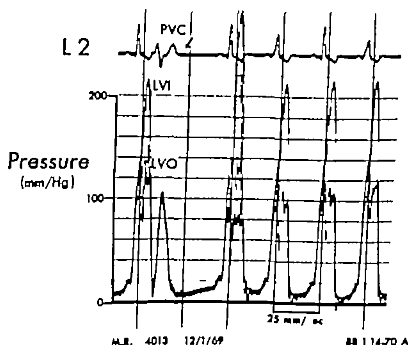


Fig 2 Simultaneous pressure tracings from left ventricular outflow tract (LVO) and left brachial artery (LBA). Following a premature ventricular contraction a fall in peak systolic pressure with narrowing of pulse pressure is noted in the immediate postextrasystolic beat.

normal aortic valve in this patient since a diastolic murmur was not noted at the time endocarditis was present. Endocarditis has been seen on the mitral valve in IHSS.

The importance of a clinical suspicion of IHSS cannot be overemphasized and complete hemodynamic evaluation should include retrograde left heart catheterization and entry into the left ventricle via the transseptal catheter. The ease of demonstration of the intracavitary left ventricular pressure gradient by this combined technique is shown in this case.

Summary

An unusual case is described in which the association of functional subvalvular left ventricular outflow obstruction, valvular aortic insufficiency, and subacute bacterial endocarditis was present. It was not possible to decide whether aortic valvular abnormality antedated the clinical episode of SBE, but the probability is that it did not. The importance of high clinical suspicion of IHSS and the usefulness of transseptal left heart catheterization are emphasized.

REFERENCES

1. Parker, D. P., Kaplan, M. A., and Connolly, E.: Coexistent aortic valvular and functional hypertrophic subaortic stenosis. Clinical, physiologic and angiographic aspects, Amer. J. Cardiol. 24:307, 1969.
2. Pare, J. A. P., Fraser, R. G., Pirozynski, W. J., Shanks, J. A., and Stubington, D.: Hereditary cardiovascular dysplasia. A form of familial cardiomyopathy, Amer. J. Med. 31:37, 1961.
3. Brachfeld, N., and Gorlin, R.: Subaortic stenosis: A revised concept of the disease, Medicine 38:415, 1959.
4. Hansen, P. F., Davidson, H. G., and Fabricius, J.: Subvalvular aortic stenosis of muscular type, Acta Med. Scand. 171:743, 1962.
5. Linhart, J. W., and Taylor, W. J.: Bacterial endocarditis in a patient with idiopathic hypertrophic subaortic stenosis, Circulation 34:595, 1966.
6. Frank, S., and Braunwald, E.: Idiopathic hypertrophic subaortic stenosis. Clinical analysis of 126 patients with emphasis on the natural history, Circulation 37:759, 1968.
7. Boiteau, G. M., and Allenstein, B. J.: Hypertrophic subaortic stenosis: Clinical and hemodynamic studies with special reference to pulse contour measurement, Amer. J. Cardiol. 8:614, 1961.
8. Soulie, P., Joly, F., and Carlotti, J.: Les stenoses idiopathiques de la chambre de chasse du ventricule gauche, Acta Cardiol. (Brux.) 17:335, 1962.

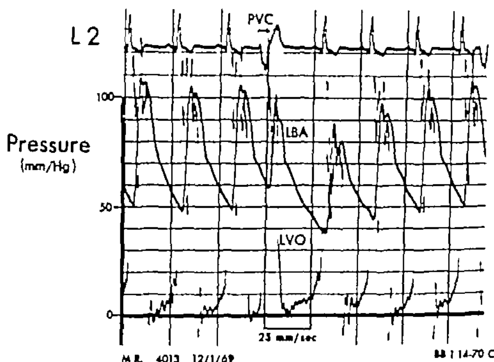


Fig 4 Note the increase in systolic gradient within the left ventricle following a premature ventricular contraction due to a rise in pressure proximal to the obstruction and a fall in pressure distal to the obstruction.

Retrograde catheterization of the left ventricle was carried out via right brachial artery cutdown. Central aortic pressure was 100/50 Pressure in the left ventricular outflow tract was 100/14 Mechanically induced catheter premature ventricular contractions resulted in a reduction in the postextrasystolic pulse pressure and a fall of 15 to 30 mm. peak systolic pressure in the brachial artery in the immediate postextrasystolic beat (Fig. 2) Transseptal catheterization by the Brockenbrough technique was carried out. Upon entering the left ventricle from the left atrium, a marked gradient was measured between the transseptal catheter in the body of the left ventricle and the retrograde catheter in the left ventricular outflow tract (Figs. 3A and 3B) The mean systolic gradient within the cavity of the left ventricle measured 63 mm. Hg and was seen to increase significantly following induced premature ventricular contractions (Fig 4)

Left ventricular cineangiography in the right anterior oblique position demonstrated marked hypertrophy of the papillary muscles with vigorous contractions. A minimal degree of mitral regurgitation was seen. Cineangiography of the aortic root in the left anterior oblique showed a tricuspid aortic valve with some deformity of the left coronary cusp. A significant degree of aortic insufficiency graded 2+ on a scale of 4 was seen. A biplane cineangiogram of the left ventricle showed marked muscular hypertrophy in the posteroanterior projection and encroachment upon the outflow tract in the lateral view

Discussion

The coexistence of major aortic insufficiency and IHSS has not been frequently described in the literature Reports describing early diastolic basal blowing murmurs are rare In a recent report[1] describing four cases of coexistent aortic valvular and functional hypertrophic subaortic stenosis some degree of aortic insufficiency was said to be present in three patients on angiographic study The angiographic demonstration of aortic insufficiency without valvular stenosis has not been previously described

The association of bacterial endocarditis with IHSS has been rarely recognized In the largest series of analyzed cases published to date Frank and Braunwald[4] reported three patients with documented endocarditis and three with suspected but not proved endocarditis in 126 cases of IHSS In one of these the aortic valve was definitely shown to be abnormal All patients had relatively severe left ventricular outflow obstruction In spite of a previous history of documented subacute bacterial endocarditis in our patient the diagnosis of IHSS was seriously considered because of the rather striking physical findings especially the association of rapid carotid upstroke with the murmur of aortic stenosis

One can only speculate as to whether endocarditis occurred on a [illegible]viously

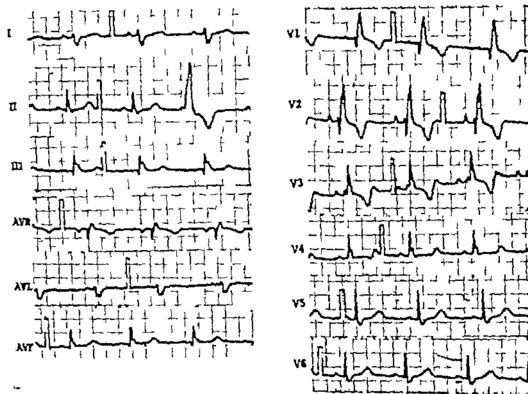


Fig. 1 The electrocardiogram showing complete right bundle branch block and a rare ventricular extrasystole.

short period of standing, a short burst of ventricular tachycardia could be induced. It was also possible to induce ventricular extrasystoles and short bursts of ventricular tachycardia by having the patient stand upright and bend forward below the horizontal position. Both of these maneuvers produced transient lightheadedness but no other symptoms. The liver was palpable 2 cm. below the right costal margin and the edge rounded Grade I.

The routine blood and urine studies were all within normal limits. Serum electrolytes were normal, serum protein electrophoresis was normal.

The electrocardiogram showed a complete right bundle branch block (Fig. 1). The routine postero-anterior chest roentgenogram revealed the cardiac size and contours to be within normal limits; however, there was a curved calcific density overlying the right ventricular area, particularly the right ventricular outflow tract (Fig. 2, *A*). On oblique and lateral roentgenograms the calcified lesion was observed to follow the course of a portion of the inflow and the entire outflow tract of the right ventricle terminating in a region just below the pulmonary trunk. In the right oblique and lateral views, a prominent bulge was present in the outflow portion of the right ventricle (Fig. 2, *B* and *C*). The resting venous pressure was within normal limits; the cardiac output at rest by the dye dilution method was within normal limits. With the patient in the recumbent position, simultaneously recorded phonocardiograms and electrocardiograms confirmed the above auscultatory phenomena (Fig. 3) and also made it possible to graphically record the induction of runs of ventricular tachycardia by left parasternal compression (Fig. 4).

While in the hospital the patient continued to complain of intermittent lightheaded spells and palpitation. There was occasional breathlessness with assumption of the recumbent position or bending forward. The use of quinidine to control the ventricular extrasystoles and runs of ventricular tachycardia produced no apparent effect. Subsequently the patient was given a combination of Dilantin, 100 mg. twice daily and propranolol, 10 mg. four times daily with apparent improvement in the disorder of rhythm, although it was still possible to induce ventricular extrasystoles by left parasternal compression. It was indicated to the patient that the findings were indicative of some form of a mass either lying within the cavity of the right ventricle or involving the anterior wall of the right ventricular musculature. It was, therefore, recommended to the patient that she undergo cardiac catheterization and angiography with the idea that surgery might be necessary shortly thereafter. The patient requested to be discharged to her home in order to make arrangements for the care of her children. She was advised to avoid all forms of heavy physical activity, to be extremely careful about the assumption of the forward bending position, and to be extremely cautious about the assumption of the recumbent position. However, while at home, about ten day following her dismissal from the hospital, she experienced sudden loss

Myxoma of the right ventricle

Report of a case with unusual findings

Theodore F Hubbard M D
Roy N Neil M D
Omaha Neb

Myxomas of the right ventricle are extremely rare tumors which produce symptoms and signs related to progressive obstruction to the outflow tract to the right ventricle and pulmonary valve[1-8] The present case is unusual and interesting in that a large heavily calcified pedunculated myxoma filled virtually the entire outflow tract of the right ventricle and was responsible for the production of variable murmurs and what we feel to be an endocardial friction rub Additionally compression in the left parasternal region would reproducibly induce ventricular tachycardia and intensification of the friction rub It was possible to visualize almost a complete outline of the tumor on the plain roentgenogram of the chest by virtue of the extensive surface calcification in the tumor

Case report

The patient, a 38-year-old housewife was admitted to the cardiovascular service for ev luation of a heart problem The patient had been told t ge 24 of the presence of a heart murm r but it was indicated that the murmur was of no consequence and that she would be able to live a normal lif The patient was always physically active and had com pleted four pregnancies without d fficulty One month prior to admission the patient noticed in creasing dyspnea with exertion and was quite short of breath with climbing one flight of stairs. She became aware of some dull left parasternal chest distress on first lying down at night. She noticed that on first assuming the recumbent position the heart would race for a short while and then abruptly slow down. Two weeks prior to admission, while standing, she suddenly lost consciousness without warning. She revived in a few minutes and there were no sequelae.

Following this there were two subsequent minor episodes during which she fell to the floor but did not completely lose consciousness. She had been aware of some intermittent palpitation. There had been no major illnesses in the past however about one and a half years ago, the patient had an episode of chest pain associated with transient hemoptysis which was diagnosed as pleurisy

Examination at the time of admission revealed a well developed, slender Caucasian woman in no immediate distress. There was no distention of the neck veins and no peripheral edema. The chest as clear to examination and chest expansion was good. The pulse rate was 70 per minute and the blood pressure was 110/70 mm. of mercury Examination of the heart revealed no evident cardiomegaly On auscultation of the heart the first and second sounds were unremarkable. There were loud to-and-fro scratchy sounds seeming very superficial and associated with ystolic and diastolic clicks throughout the precordial area. These sounds were most intense in the second nd third interspaces at the left sternal margin and they could be altered substantially in intensity by changes in body position. In the recumbent position moderate left parasternal compression greatly intensified both the systolic and diastolic components of these sounds, and with slight fu ther compression a run of ventricular extrasystoles could be produced and sustained so long as the compressio was maintained. When the patient would assume the recumbent position after

From the Cardiopulmonary Laboratory and Department of Pathology Bishop Clarkson Memorial Hospital, Omaha, Neb.
Received for publication Feb. 25, 1970.
Reprint requests to: Theodore F Hubbard, M.D., 639 The Doctors Building, Omaha, Neb. 68131.

Fig. 2, *B* and *C*. For legend see opposite page.

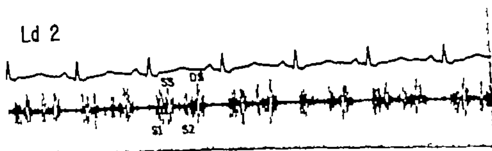


Fig. 3. Phonocardiogram recorded in the third left intercostal space at the left sternal margin showing systolic and diastolic sounds as ell as clicks in systole and diastole.

failure. Syncopal episodes and ventricular arrhythmias are commonly seen with change of position related to intermittent, near complete obstruction of the right ventricular outflow tract, pulmonary valve, or pulmonary artery. Variable low grade fever has been observed occasionally.

The most characteristic physical findings are ejection type systolic murmurs in the pulmonic area often varying from day to day or with change of position. Additional short presystolic or early diastolic sounds have been observed and recorded. The electrocardiogram has usually been normal occasionally showing right ventricular hypertrophy or right bundle branch block. The roentgen appearance of the heart has not shown characteristic abnormalities



Fig. A B and C The chest roentgenogram in the posteroanterior (A) and right (B) and left anterior oblique projections (C) In all three projections an outline of the distal three quarters of the tumor is visualized by virtue of the heavy calcification of the surface of the tumor The tumor fills a portion of the inflow tract and most of the outflow tract of the right ventricle extending to the area of the pulmonary valve. In the right anterior oblique projection there is prominence of the right ventricular outflow tract and base of the pulmonary trunk.

of consciousness while bending over and lifting a heavy object and one week following this episode while bending forward, she suddenly lost consciousness, became intensely cyanotic, stopped breathing, and could not be revived At our request the family physician obtained the postmortem specimen of the heart and pericardial sac for review by our pathology department.

The pericardium and epicardium were grossly normal. There was a very prominent bulge in the entire outflow portion of the right ventricle. The heart weighed 325 grams after fixation. On viewing the pulmonary valve through the open pulmonary artery there was a large calcified tumor mass bulging into the pulmonary valve area. With opening the right ventricle there was a large tumor arising from the inferior surface of the anterior cusp of the tricuspid valve and several of the attached chordae and extending the entire length of the right ventricle to the pulmonary valve. The tumor mass measured 90 by 30 by 25 mm. The proximal portion was firm gray-black, and glistening. The distal three quarters of the tumor was grossly irregular and most of the surface was calcified (Fig 5) The subpulmonic region of the right ventricle showed irregular thickening of the endocardium. The pulmonary valve cusps were shortened and somewhat thickened. There appeared to be mild dilatation of the right atrium the left heart musculature and valves were all normal. The coronary arteries were normal. Microscopic examination of the tumor removed from the right ventricle revealed it to be covered largely by endothelium At the base of the tumor near its attachment the ground work was amorphous and myxomatous. Near the area where it was removed from the tricuspid valve there were stellate cells typical of myxomatous tissue, and more distally there were large multinucleated cells (Fig 6) There were also lymphocytes, plasma cells, and scattered neutrophils. There were scattered small capillaries. The entire distal two thirds of the tumor was infarcted and consisted of calcium and eosinophilic necrotic collagen tissue.

Discussion

The rare myxomas of the right ventricle have usually produced symptoms and signs related to progressive obstruction of the outflow tract of the right ventricle and pulmonary artery with or without associated symptoms related to pulmonary artery embolization by thrombi or fragments of tumor tissue Symptoms consist of dyspnea and variable degrees of right ventricular

Fig. 2, *B* and *C*. For legend see opposite page

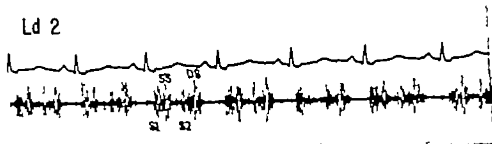


Fig. 3. Phonocardiogram recorded in the third left intercostal space at the left sternal margin showing systolic and diastolic sounds as well as clicks in systole and diastole.

failure. Syncopal episodes and ventricular arrhythmias are commonly seen with change of position related to intermittent, near complete obstruction of the right ventricular outflow tract, pulmonary valve or pulmonary artery. Variable low grade fever has been observed occasionally.

The most characteristic physical findings are ejection type systolic murmurs in the pulmonic area often varying from day to day or with change of position. Additional short presystolic or early diastolic sounds have been observed and recorded. The electrocardiogram has usually been normal occasionally showing right ventricular hypertrophy or right bundle branch block. The roentgen appearance of the heart has not shown characteristic abnormalities

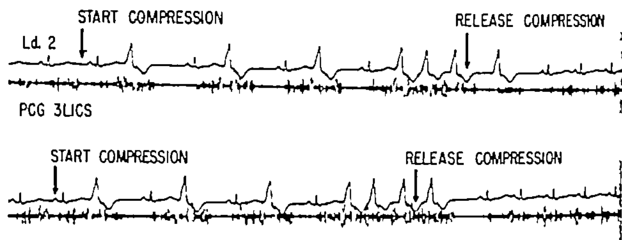


Fig. 4. Lead II of the electrocardiogram and the phonocardiogram recorded in the second left intercostal space at the left sternal margin showing the reproducible effects of left parasternal compression in causing an intensification of the abnormal systolic and diastolic sounds and a run of ventricular tachycardia stopping with the release of the compression.



Fig. 5. Right ventricle and pulmonary valve opened to show the tumor coursing from the inferior aspect of the tricuspid valve through the right ventricle to the pulmonary valve.

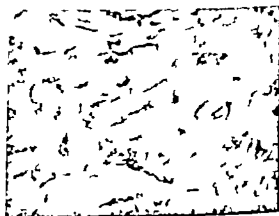


Fig. 6. Photomicrograph of the tumor (×100). The tumor consists of single cells and syncytial cells, some of which have cytoplasmic processes. Many of the cells have round to oval nuclei. The stroma is myxoid and contains mucin.

except for variable dilatation of the right ventricular outflow tract and pulmonary trunk. From a laboratory standpoint some elevation of the sedimentation rate, abnormalities in the serum proteins and polycythemia have been described.

Our patient showed symptoms similar to what have been described although there was no evidence at the time of admission of right heart failure. The only distinctive physical finding in our patient was entirely characteristic of a friction rub although some of the auscultatory findings were undoubtedly typically murmurs of variable obstruction at the pulmonary valve ring and some pulmonic valvular regurgitation. However, it is felt that most of these auscultatory abnormalities were related to the actual rubbing of the heavy calcific mass in the outflow tract of the right ventricle during systole and diastole producing what we have chosen to consider an endocardial friction rub. The sounds were of relatively low frequency, coarse and scratchy and appeared to be very superficial in the left parasternal region. There were variable additional clicking sounds in systole and diastole. These sounds were greatly intensified by pressure in the left second and third interspaces. With this compression maneuver the sounds became very loud, coarse and grating and with maintenance of this maneuver of the firmer pressure, ventricular extrasystoles and runs of ventricular tachycardia were induced which

we have interpreted as also being due to endocardial stimulation with rubbing of the ventricular endocardium by the calcified tumor. An alternate explanation might be that the compression maneuver simply aggravated the outflow tract obstruction, intensified systolic and diastolic murmurs, and produced symptomatic extrasystoles by acute right ventricular dilatation. However, the timing of the sounds makes this explanation seem to us less likely.

Last, the roentgenographic appearance of the tumor was such as to outline about three fourths of its total course in the right ventricle and in retrospect would allow a ready and conclusive diagnosis of a calcified right ventricular tumor. However, the combination of the physical findings and x-ray appearance were such that prior to the patient's death—although a calcified right ventricular tumor seemed the most likely explanation for all these phenomena—we felt that some form of calcifying lesion in the anterior wall of the right ventricle producing a friction rub and symptomatic paroxysmal ventricular arrhythmias and extrasystoles was an alternate explanation. It is presumed that the sudden death in this patient was related to sudden profound and unremitting obstruction of the pulmonary valve and right ventricular outflow tract or the induction of sudden ventricular fibrillation.

In this case prompt confirmatory studies by right heart catheterization and right ventricular angiography followed by surgical removal of the tumor might have saved the patient's life.

Summary

A case of myxoma of the right ventricle is presented in which the patient exhibited many of the usual clinical symptoms which have previously been described. She exhibited syncopal episodes and bursts of ventricular tachycardia, and the clinical course terminated in sudden death. The patient presented unusual auscultatory phenomena which we have tentatively attributed to the rhythmic rubbing during the cardiac cycle of the large calcific tumor mass against the endocardium of the right ventricular outflow tract. An additional unusual feature was the appearance of an outline of most of the tumor in the right ventricle by the heavy calcification in the wall of the infarcted tumor.

We wish to thank Mrs. Kay Green and Miss Rose Reynolds for their invaluable assistance in the preparation of this manuscript.

REFERENCES

1. Czapek (1891): Quoted by Husten, K.: Über Tumoren und Pseudotumoren des Endocards, Beitr. Path. Anat. 71:132, 1923.
2. Kishimoto, M., and Sakaibori, S.: Primary tumor of the heart: Report of a case with myxofibroma of the right ventricle, Amer. Heart J. 57:69, 1959.
3. Michaud, P., Saubier, E., Termet, H., Maret, G., Gravier, J., and Dalloz, C.: Exérèse sous circulation extra-corporelle d'un myxome du ventricule droit, Lyon Chir. 56:788, 1960.
4. Donatelli, R., Gori, G., and Pellegrini, A.: Sul Myxoma cordis, Rilievi anatomo-patologici e clinico-diagnostici su tre case, Minerva Cardioangiol. 9:467, 1961.
5. MacRae, F. R., and Gales, M.: Myxoma of the right ventricle of the heart, Canad. Med. Ass. J. 85:435, 1961.
6. Gottsegen, G., Wessely, J., Arvay, A., and Temesvari, A.: Right ventricular myxoma simulating pulmonic stenosis, Circulation 27:95, 1963.
7. Dooben, D. J., Greer, J. W., Thoro, N., and Timmes, J. J.: Emergency excision of a myxoma of the right ventricle which was obstructing the right ventricular outflow tract, J. Thorac. Cardiovasc. Surg. 47:342, 1964.
8. Sakakibara, S., Osawa, M., Sooji, K., Hashimoto, A., Gomi, H., Miyamoto, A. M., and Takao, A.: Myxoma of the right ventricle of the heart, Amer. Heart J. 69:382, 1965.

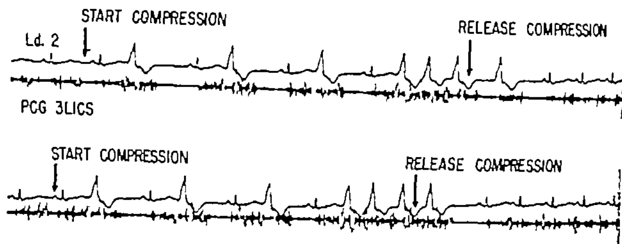


Fig. 4. Lead II of the electrocardiogram and the phonocardiogram recorded in the second left intercostal space at the left sternal margin showing the reproducible effects of left parasternal compression in causing an intensification of the abnormal systolic and diastolic sounds and a run of ventricular tachycardia stopping with the release of the compression.



Fig. 5. Right ventricle and pulmonary valve opened to show the tumor coursing from the inferior aspect of the tricuspid valve through the right ventricle to the pulmonary valve.

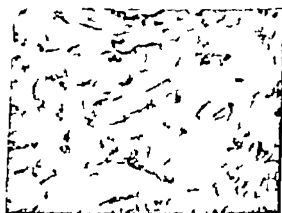


Fig. 6. Photomicrograph of the tumor (×100). The tumor consists of single cells and syncytial cells, some of which have cytoplasmic processes. Many of the cells have round to oval nuclei. The stroma is myxoid and contains mucin.

except for variable dilatation of the right ventricular outflow tract and pulmonary trunk. From a laboratory standpoint some elevation of the sedimentation rate, abnormalities in the serum proteins, and polycythemia have been described.

Our patient showed symptoms similar to what have been described although there was no evidence at the time of admission of right heart failure. The only distinctive physical finding in our patient was entirely characteristic of a friction rub although some of the auscultatory findings were undoubtedly typically murmurs of variable obstruction at the pulmonary valve ring and some pulmonic valvular regurgitation. However, it is felt that most of these auscultatory abnormalities were related to the actual rubbing of the heavy calcific mass in the outflow tract of the right ventricle during systole and diastole producing what we have chosen to consider an endocardial friction rub. The sounds were of relatively low frequency, coarse and scratchy, and appeared to be very superficial in the left parasternal region. There were variable additional clicking sounds in systole and diastole. These sounds were greatly intensified by pressure in the left second and third interspaces. With this compression maneuver the sounds became very loud, coarse and grating, and with maintenance of this maneuver of the firmer pressure, ventricular extrasystoles and runs of ventricular tachycardia were produced which

chest x-ray showed bilateral pleural effusions and cardiomegaly compatible with congestive heart failure. An electrocardiogram taken on admission (Fig. 1 *A*) showed rate of 83 P R interval 0.16 seconds, QRS duration of 0.10 seconds, and QRS axis minus 30 degrees. S-T segments were depressed in Leads I and V and elevated in Leads III and V. A Q wave was present in Leads III and V. The S wave in V through V was deep. S-T segments in V and V were depressed. On the ninth hospital day S-T segments in Leads III and V were elevated. Also S-T segments in V through V were elevated. On day 12 (Fig. 1 *B*) it was noted that the duration of QRS complex had increased to 0.12 second. Three blood cultures were negative.

The patient was given morphine which controlled his pain. Digitoxin was continued. He had been receiving cyclothiazide and potassium chloride but was switched to chlorothiazide. A presystolic gallop was noted on the second hospital day. He was dyspneic and had rales at both bases. On day 3 he was given an injection of 2 c.c. of meralluride. There was no diuresis. On day 4 thoracentesis was performed, and 600 c.c. of "tea-colored" turbid fluid with specific gravity of 1.008 was removed from the right pleural space. Cultures and cytologic studies were negative. The patient was started on acetazolamide. On day 6 the patient developed a to and fro friction rub which was heard in the epigastric region and along the left sternal border. On day 8 the serum sodium was 125 mEq. per liter, serum potassium 5.0 mEq. per liter, serum chloride 78 mM per liter and serum CO_2 22.8 mM per liter. On day 9 the urine output which had been 600 to 800 c.c. daily dropped to zero. The blood urea nitrogen (BUN) was 43 mg. per cent. Two hundred cubic centimeters of urine were obtained on catheterization. The patient was given dextrose and water and potassium chloride and gradually resumed urine production. An intravenous pyelogram (IVP) showed excellent visualization of the kidneys with normal collecting system. On day 12 the urine volume had returned to 660 c.c. Urinary electrolytes were sodium 3 mEq. per liter, potassium 39 mEq. per liter, chloride 20 mEq. per liter and urea nitrogen 800 mg. per cent. The serum calcium was 9.0 mg. per cent, serum phosphorus 3.1 mg. per cent, serum alkaline phosphatase 11 units, and serum acid phosphatase 1.0 unit. Total serum bilirubin was 0.7 mg. per cent and blood uric acid 11.5 mg. per cent. A femoral artery puncture was performed. Oxygen saturation was 84 per cent, CO_2 was 16.79 mM per liter, PCO_2 27.8 mm. Hg, and the pH was 7.46. On the thirteenth hospital day the patient developed ventricular fibrillation and died.

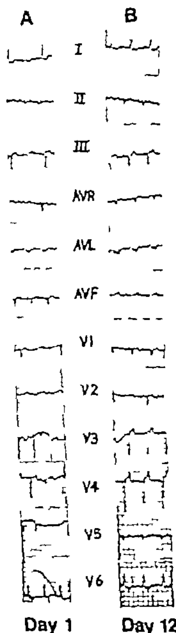


Fig. 1 *A*. The admission electrocardiogram (ECG) shows QRS axis of minus 30 degrees, QRS duration 0.10 second, and P R interval of 0.16 second. Note the S-T segment changes. *B*. ECG on twelfth hospital day shows prolongation of QRS complex to 0.12 second.

Discussion

DR. PAGE: The patient under consideration was a 61 year-old man who presumably had been in excellent health until six months prior to admission. Five years earlier however an application for a life insurance policy resulted in the assessment of an additional premium. He was asymptomatic until six months ago when he developed fatigue, exertional dyspnea, and what might be interpreted as angina pectoris, all of which were progressive, and finally he was forced to quit work because

Clinical pathologic conference

Robert H Kirschner M D
Francis L Archer M D
Malcolm Page M.D *
Jerry Pelasnick M.D **
Seymour Glagov M.D
Chicago Ill

Case presentation

A 61 year-old white male sign painter was admitted to the University of Chicago Hospitals with chest pain following three months of progressively increasing shortness of breath. On the morning of his admission the patient developed severe and persistent retrosternal and precordial pressure pain while shaving There was no radiation of the pain. When he became markedly dyspneic he was brought to the hospital He died thirteen days later

His health had been excellent until six months prior to admission when he began to experience mild fatigue, dyspnea and brief episodes of precordial pain following the lifting of heavy objects. Symptoms became more severe until severe fatigue and dyspnea on exertion required him to discontinue his work three months prior to admission. He was hospitalized elsewhere with symptoms of acute congestive heart failure, which improved with digitalization Following discharge he experienced frequent palpitations, anorexia, weight loss, constipation, and a cough productive of whitish sputum A life insurance policy purchased five years previously required an additional premium, supposedly because of his age. The patient's mother had died of heart disease at the age of 70 and his father had died in congestive failure at the age of 63

On admission the patient was markedly dyspneic but not cyanotic. He was well developed and well nourished. Respiratory rate was 36 per minute and shallow pulse 82 blood pressure 100/70 and temperature 37° C. He complained of marked and persistant precordial pressure pain without radiation. His neck veins were not distended when sitting at a 45 degree angle. There was dullness to percussion and diminished breath sounds in both lung bases No rales could be heard. The apex beat of the heart was in the fifth left intercostal space in the midclavicular line. There was a systolic retraction at the apex. A systolic thrill was palpable in the second, third and fourth right interspaces. S_1 and S_2 were absent in the aortic area. S_2 in the pulmonic area was loud S and S were absent at the apex. There was a Grade III/VI harsh systolic decrescendo, not typical ejection murmur heard in the aortic area that radiated over the entire precordium. This murmur could also be heard in the neck. A faint early diastolic murmur was heard over the left precordium The liver was palpable two finger-breadths below the right costal margin. There was no peripheral edema.

Initial white blood cell count was 13 000/mm.³ and the differential count was normal Hemoglobin was 13 Gm per cent. Urinalysis revealed no abnormalities specific gravity was 1 023 Fasting blood sugar was 128 mg per cent. Serum sodium was 134 mEq per liter serum potassium 5.2 mEq per liter and serum chloride 85 mM per liter The total plasma protein was 6.5 Gm. per cent with albumin 3 4 Gm. per cent and globulin 3 1 Gm. per cent. Blood urea nitrogen was 16 mg per cent. Total serum cholesterol was 170 mg per cent with the esters comprising 110 mg per cent. Serum enzymes were as follows: on admission, lactate dehydrogenase (LDH) 1 000 units, serum glutamic oxalacetic transaminase (SGOT) 38 units, and serum glutamic pyruvic transaminase (SGPT) 26 units. On the fourth day LDH was 410 units, SGOT 21 units, and SGPT less than 5 units. On day 11 LDH was 640 units, SGOT 105 units, and SGPT 169 units. The sedimentation rate was 33 mm. on the eighth day and on day 11 46 mm. per hour An admission

From the Departments of Pathology Medicine and Radiology University of Chicago, Chicago, Ill.
The conference was arranged and directed by Dr Glagov
Reprint requests to Dr. Seymour Glagov Department of Pathology University of Chicago Hospitals, 950 East 59th St., Chicago, Ill. 60637
*Mary Imogene Bassett Hospital, Cooperstown, N Y
**Presbyterian-St. Luke Hospital, Chicago, Ill.

chest x-ray showed bilateral pleural effusions and cardiomegaly compatible with congestive heart failure. An electrocardiogram taken on admission (Fig. 1 *A*) showed a rate of 83, P-R interval 0.16 seconds, QRS duration of 0.10 seconds, and QRS axis minus 30 degrees. S-T segments were depressed in Leads I and V[illegible], and elevated in Leads III and V[illegible]. A Q wave was present in Leads III and V[illegible]. The S [illegible] in V[illegible] through V[illegible] was deep. S-T segments in V[illegible] and V[illegible] were depressed. On the ninth hospital day S-T segments in Leads III and V[illegible] were elevated. Also S-T segments in V[illegible] through V[illegible] were elevated. On day 12 (Fig. 1, *B*) it was noted that the duration of QRS complex had increased to 0.12 second. Three blood cultures were negative.

The patient was given morphine which controlled his pain. Digitoxin was continued. He had been receiving cyclothiazide and potassium chloride but was switched to chlorothiazide. A presystolic gallop was noted on the second hospital day. He was dyspneic and had rales at both bases. On day 3 he was given an injection of 2 c.c. of meralluride. There was no diuresis. On day 4 a thoracentesis was performed, and 600 c.c. of "tea-colored" turbid fluid with specific gravity of 1.008 was removed from the right pleural space. Cultures and cytologic studies were negative. The patient was started on acetazolamide. On day 6 the patient developed a to-and-fro friction rub which was heard in the epigastric region and along the left sternal border. On day 8 the serum sodium was 125 mEq. per liter, serum potassium 5.0 mEq. per liter, serum chloride 78 mM per liter, and serum CO_2 22.8 mM per liter. On day 9 the urine output which had been 600 to 800 c.c. daily dropped to zero. The blood urea nitrogen (BUN) was 43 mg. per cent. Two hundred cubic centimeters of urine were obtained on catheterization. The patient was given dextrose and water and potassium chloride and gradually resumed urine production. An intravenous pyelogram (IVP) showed excellent visualization of the kidneys with normal collecting systems. On day 12 the urine volume had returned to 660 c.c. Urinary electrolytes were sodium 3 mEq. per liter, potassium 39 mEq. per liter, chloride 20 mEq. per liter, and urea nitrogen 800 mg. per cent. The serum calcium was 9.0 mg. per cent, serum phosphorus 3.1 mg. per cent, serum alkaline phosphatase 11 units, and serum acid phosphatase 1.0 unit. Total serum bilirubin was 0.7 mg. per cent and blood uric acid 11.5 mg. per cent. A femoral artery puncture was performed. Oxygen saturation was 84 per cent, CO_2 was 16.79 mM per liter, PCO_2 27.8 mm. Hg, and the pH was 7.46. On the thirteenth hospital day the patient developed ventricular fibrillation and died.

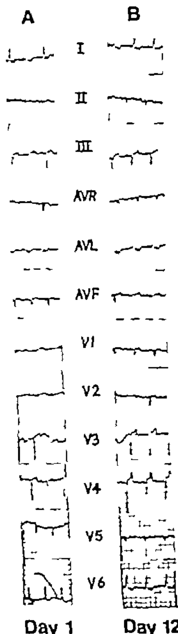


Fig. 1. *A*, The admission electrocardiogram (ECG) shows QRS axis of minus 30 degrees, QRS duration 0.10 second, and P-R interval of 0.16 second. Note the S-T segment changes. *B*, ECG on twelfth hospital day shows prolongation of QRS complex to 0.12 second.

Discussion

DR. PAGE: The patient under consideration was a 61-year-old man who presumably had been in excellent health until six months prior to admission. Five years earlier, however, an application for a life insurance policy resulted in the assessment of an additional premium. He was asymptomatic until six months ago when he developed fatigue, exertional dyspnea, and what might be interpreted as angina pectoris, all of which were progressive, and finally he was forced to quit work because

of the severity of the symptoms He was admitted to another hospital in acute heart failure and treated with digitalis. From that time on he manifested symptoms of congestive heart failure culminating in an acute episode of persistent retrosternal and precordial pressure pain which prompted his admission to this hospital He was admitted in all likelihood with a presumptive diagnosis of acute myocardial infarction

This history however leads me to the conclusion that he did not have uncomplicated coronary artery disease with myocardial infarction The fact that an additional premium was assessed on his life insurance policy suggests very strongly that he had (1) hypertension (2) a heart murmur (3) an abnormal electrocardiogram or (4) an abnormal urinalysis at least five years ago Coronary artery disease might result in anginal symptoms leading to infarction but the symptoms of fatigue and exertional dyspnea indicate heart failure If heart failure were due to coronary artery disease he must have had previous myocardial damage I believe that heart failure developing under such circumstances would most likely have come to a physician's attention earlier and not have brought the patient to the hospital suddenly in acute heart failure For similar reasons I am inclined to exclude hypertensive heart disease and chronic renal disease There remains then valvular heart disease which I believe may explain the clinical history quite adequately

Physical examination clarified the situation for us. It revealed the classic findings of aortic stenosis. While the patient had a diastolic murmur audible along the left sternal border I believe that we can be confident that he did not have significant aortic regurgitation The left ventricle was not massively dilated the diastolic blood pressure was 70 mm and peripheral signs of aortic insufficiency were not described In addition to the cardiac findings the patient was markedly dyspneic on admission but not cyanotic. The blood pressure was 100/70 and apparently he did not exhibit the restlessness or cold mottled clammy skin associated with shock which frequently may accompany myocardial infarction There were signs of fluid in both lung bases but no rales were heard His liver was enlarged but no peripheral edema was demonstrated Perhaps we should discuss the x rays at this time



Fig 2 Frontal chest film taken on the eighth hospital day shows cardiomegaly pulmonary venous congestion and infiltrates in the left upper lobe and at the base of the right lung

DR PETASNICK The admission chest film showed cardiomegaly bilateral pleural effusions and changes in the lungs suggestive of peripheral pulmonary venous congestion The film taken several days later (Fig 2) showed some clearing at the left base, and infiltrates in the left upper lung field and at the right base The hila and vessels are prominent The patient is still in congestive failure On the last examination there were small bilateral effusions and the changes indicative of congestive failure were still present in the lungs

DR PAGE Are there discernible calcifications in the aortic or mitral valves?

DR. PETASNICK No I can not see any valve calcifications nor is there any evidence of aortic dilatation or calcification

DR PAGE I believe that we have a patient with the classical features of aortic stenosis. Aortic stenosis produces obstruction to the flow of blood from the left ventricle As a result there is incomplete emptying of the left ventricle and cardiac out

put falls. Incomplete emptying results in an increase in intraventricular pressure. The heart compensates for the fall in cardiac output by a prolongation of systolic ejection. As time goes by there is further compensation by an increase in the period of isometric contraction and an even greater prolongation of systolic ejection. Under these circumstances the heart can maintain cardiac output, at least under sedentary conditions. But there comes a time when the cardiac output cannot be sufficiently increased to meet the demands of exercise. Consequently easy fatigability and exertional dyspnea arise. These changes come about gradually and the ventricle is mainly hypertrophied rather than dilated as we have observed in our patient. When heart failure does occur it usually does so suddenly as happened to our patient when he was admitted to another hospital in acute heart failure. Coronary artery disease frequently accompanies aortic stenosis and may lead to myocardial infarction. Nevertheless, it is not uncommon to encounter myocardial infarction without coronary occlusion in aortic stenosis. The blood supply to the myocardium is directed from the epicardial to the endocardial surface and under conditions of hypertrophy and increased work load there is a relative deficiency of blood supply to the subendocardium. In addition the prolonged isometric contraction, the increased intraventricular pressure, and prolonged systolic ejection all tend to decrease systolic coronary filling and shorten diastole thereby reducing coronary blood flow. Such circumstances then may lead to the symptoms of angina or even subendocardial or transmural infarction without actual coronary occlusion.

Patients with pure aortic stenosis have a relatively good prognosis in comparison with patients who have aortic insufficiency or mitral stenosis. The average age of death is close to 60 years as compared to 40 years for patients with mitral stenosis. This relatively favorable prognosis depends on the maintenance of compensation. In a series of patients with aortic stenosis studied by Contratto and Levine,[1] the prognosis became extremely poor and the disease rapidly progressive once heart failure developed. The occurrence of death for instance was noted on the average of 23 months after the onset of dyspnea 9 months after the onset of edema 6 months after the onset of rales in the lungs, and 4 months after the first attack of pulmonary edema. Our patient lived three and a half months after his first attack of pulmonary edema. Sudden death is encountered frequently in aortic stenosis and may be due to myocardial infarction with or without coronary occlusion, pulmonary edema, cardiac arrhythmia cerebral infarction due to abrupt or extreme diminution of cardiac output thromboembolic disease including embolism to the coronary artery or a hypersensitive carotid sinus reflex. There has been at least one case reported of an occluding thrombus over a stenotic aortic valve. Our patient then exhibited the classical features of aortic stenosis. He lived to an age of 61 years. He had progressive symptoms of easy fatigue, exertional dyspnea, and finally chest pains on exertion and he developed acute heart failure suddenly finally dying three and a half months later of a cardiac arrhythmia.

Let us examine the laboratory data available to us and the hospital course to see if we can determine the cause of his demise. He was not anemic. The white count was slightly elevated but the differential was normal. The urinalysis indicated good renal function at the time of admission and the BUN was normal. The electrocardiogram with elevation of the S-T segments in Leads III and V_F with reciprocal depression in Leads I and V_L suggested posterior wall ischemia, but the S-T segment elevation persisted over a twelve day period without definite evidence of changes of infarction. The serum LDH was 1,000 units on admission. It fell to normal on the fourth hospital day and increased slightly on the eleventh day. The SGOT and SGPT were normal until the eleventh day. On the basis of the electrocardiographic and serum enzyme findings, I am inclined to think that he did not have a recent transmural myocardial infarction. I interpret the elevation of all serum enzymes on the eleventh day as due to liver congestion and hypoxia. On the fourth hospital day the patient underwent thoracentesis. The fluid removed was tea

colored and turbid Immediately this observation caught my attention because the transudates of congestive heart failure are straw-colored Traumatic taps of course are pink or red-colored The operator made no mention of a traumatic procedure or that the color faded progressively as the volume of fluid removed increased The serum bilirubin was normal at the time of the procedure Cell counts in the fluid are not reported and therefore I must conclude that the tea-colored fluid represents old bloody fluid This immediately suggests malignancy or pulmonary emboli I can find no evidence for malignancy in this patient Indeed cytological study of the fluid failed to demonstrate malignant cells On the other hand pulmonary emboli occur commonly in medical practice Pulmonary embolism is not synonymous with pulmonary infarction Embolism is much more common Most of the signs that we think of in association with these events such as pleuritic pain hemoptysis fever and x ray shadows are actually signs of infarction rather than pulmonary vascular occlusion and thus will be absent if infarction doesn t follow embolism Embolism results in an area of lung which is ventilated but not perfused and leads to hyperventilation and oxygen desaturation depending of course upon the total area of lung involved In this case we have arterial blood studies available to us. The oxygen saturation was 84 per cent and pCO_2 was low these findings are quite compatible with hyperventilation and decreased gas exchange The demonstration of oxygen desaturation is a useful tool in differentiating congestive heart failure from pulmonary disorders for oxygen desaturation does not occur in pure congestive heart failure In this condition cyanosis occurs as a result of stasis and not desaturation The protocol didn t indicate it, but there were areas of infiltration on the chest x ray as reported by the radiologist I believe therefore that we have good evidence that our patient had bilateral multiple pulmonary emboli He did develop a to and fro friction rub on the sixth hospital day which we usually attribute to pericarditis accompanying myocardial infarction but such friction rubs do occur in patients with pulmonary emboli The elevation of the serum LDH to 1 000 units with a normal SGOT on admission also supports this contention

Now let s consider the renal and electrolyte problem He was receiving in addition to digitoxin cyclothiazide with potassium chloride and subsequently chlorothiazide, meralluride and finally acetazolamide. In the course of one week his serum sodium fell from 134 to 125 mEq per liter and the BUN rose to 43 mg per cent. This was thought by the service to be a prerenal azotemia and I certainly agree The urinary sodium was very low and the ratio of urine urea nitrogen to serum urea nitrogen was approximately 20 The urinary output fell to zero but upon catheterization 200 c c. of urine was obtained I believe that the prerenal azotemia was due to decreased cardiac output with decreased renal blood flow and decreased glomerular filtration Renal artery occlusion due to thrombosis or emboli, of course might be a cause of prerenal azotemia but I think that this was probably not the case here Renal artery occlusion would have to be bilateral to produce azotemia and although such events have been described I think it must be rather uncommon The intravenous pyelogram was normal although the timing here is quite important The exact time of these events is not clear to me from the protocol Early after occlusion of course the kidneys may fail to visualize although visualization may return within a very few days unless complete infarction results I suppose that in the presence of compromised renal function an embolus to one renal artery could produce azotemia but it is difficult to make that diagnosis in this particular patient. We should always keep the possibility of postrenal azotemia in mind For example in men confined to bed with congestive heart failure an edematous prostate may lead to renal failure but such was probably not the case here as only 200 c c of urine was removed by catheterization Another possibility exists since the serum uric acid was 11 mg per cent This increase could have been due to renal failure The chlorothiazide group of drugs may increase the serum uric acid and even precipitate an acute attack of gout. Under circumstances of decreased urine flow such as we have encountered

here uric acid might crystalize in the renal tubules. I would not be surprised if uric acid crystals were found in the renal tubules by the pathologist.

One more possible diagnosis needs to be considered. Bacterial endocarditis can present many features noted in this case. However there are many points against it. The patient was neither anemic, nor febrile. There were no cutaneous petechiae mucosal hemorrhages, or Janeway lesions. The spleen was not palpable and microscopic hematuria was not described. In addition three blood cultures were negative. While endocarditis does occur in approximately 10 per cent of patients with aortic stenosis, it seems to be less common in the absence of aortic insufficiency.

Our patient died of cardiac arrhythmia. This is not uncommon in aortic stenosis. Under such circumstances I think we have to consider a coronary artery embolus but out of necessity this must be an autopsy diagnosis. He had ample predisposition to cardiac arrhythmia however. An ischemic myocardium with an increased work load subjected to hypoxia azotemia electrolyte disturbance, and drugs such as digitalis and diuretic agents may be predisposed to cardiac arrhythmias. I believe in summary that the patient had the classical features of aortic stenosis. I believe we will find that he died with multiple pulmonary emboli and that he had evidence of myocardial ischemia and fibrosis but probably without transmural infarction.

DR. ROBERT G. PAGE* There is a QS wave in Lead III and in V which is suggestive of old posterior wall damage. The fact that the S-T segments are depressed in Leads I and V in particular and elevated in III and V would make one consider a posterior wall infarction however these electrocardiograms remained essentially stable throughout the hospital course. I would also like to point out that the murmur was not considered to be wholly typical of aortic stenosis by many of the physicians who examined the patient. I found some rather interesting discussions about this in the patient's record. Some observers felt that there might be a ruptured interventricular septum secondary to a myocardial infarction and another suggested that perhaps there had been a rupture of a cusp. If this had happened I think one would have found a more prominent diastolic component and a wider pulse pressure.

QUESTION *Is it possible that the patient had an atrial myxoma?*

DR. M. PAGE If it were an atrial myxoma we would expect evidence that the symptoms altered with changes in body position. If a patient with a myxoma leaned forward for instance he might precipitate sudden acute dyspnea and even pulmonary edema. I don't think that we have any evidence of this here. Myxomas of the left atrium give classical features of mitral stenosis. I did not think our patient presented either the clinical course or the signs of mitral stenosis.

DR. ARCHER The patient's disease was confined almost entirely to the cardiovascular system with the single exception of some chronic changes in the lungs. There were about 1500 c.c. of clear tea-colored fluid in the right pleural cavity and about half that amount in the left pleural cavity.

Acute fibrinous pericarditis was found with fresh deposits of fibrin adherent over wide areas of the epicardium including the atrial surfaces. (Fig. 3A.) Culture of the exudate did not yield any bacterial growth nor did blood cultures taken post mortem. Fig. 3B illustrates the character of the inflammatory reaction which consisted of fibrin overlying recently formed granulation tissue and infiltrated by lymphocytes, with only a few neutrophiles. It is estimated that the pericarditis must have been present for at least one to two weeks.

The left ventricle was dilated as well as hypertrophied and the heart weighed 655 grams. There was severe deformity and calcification of the aortic valve, with marked narrowing of the valve opening (Fig. 4). The valve cusps were thickened and rigid and were so distorted as to make recognition of the individual cusps no longer possible. There was no inflammatory reaction in the valve substance or in the adjacent myocardium. The aorta was not particularly dilated and although there were a few plaques in the ascending and abdominal aorta, the degree of aortic arteriosclerosis was not severe. Although

*Associate Dean and Associate Professor of Medicine; presently Dean, Medical College of Ohio.

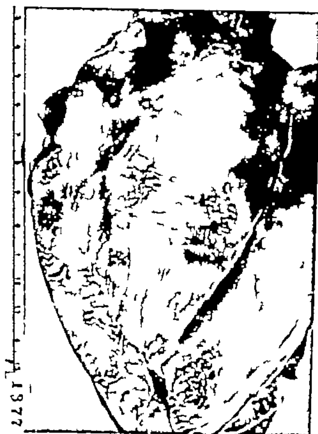


Fig 3A Fibrinous pericarditis. Note the thick shaggy fibrin deposits adherent to the epicardium.

there was some narrowing of the orifices of both coronary arteries both were patent. There was a moderate degree of coronary artherosclerosis with a focal segment of narrowing and calcification of the anterior descending branch of the left coronary artery 1 5 cm distal to its origin The main branches of the coronary arteries were otherwise patent and their distribution was normal

The principal lesion in the myocardium was acute infarction Poorly circumscribed areas of yellow and purple discoloration could be seen through the endocardium and were most obvious over the interventricular septum the posterior papillary muscle and the anterior wall Sampling of the myocardium for microscopic study however revealed the infarction to be even more extensive and patches of myocardial necrosis were seen in every sample taken from base to apex in all regions of the left ventricle Although wide areas of the heart muscle were affected the distribution of the infarct was unusual in that necrosis was confined to a narrow bandlike subendocardial zone (Fig 5) Adjacent myocardial fibers were swollen and vacuolated an appearance which has been described as myocytolysis and which is thought to be



Fig 3B Microscopic appearance of the lesion showing acellular areas containing fibrin overlying recently formed granulation tissue intermixed with chronic inflammatory cells. (See Fig 3A.)

due to ischemia. The endocardium was smooth and intact and the outer layers of the myocardium were spared although they contained scattered areas of fine fibrosis of the type usually associated with chronic reduction of blood flow.

There was little evidence of cellular inflammatory response in the area of subendocardial infarction. This is the usual finding when tissue death has been the final event in a gradual degeneration due to progressive ischemia resulting in modification of the usual cellular reaction to dead tissue. In the posterior papillary muscle on the other hand the infarction was more extensive involving the whole thickness of the muscle, and there was an intense neutrophilic inflammatory response, indicating a more sudden and probably more recent onset.

In the lungs we found only moderate chronic passive congestion with slight fibrosis of alveolar septa. There were no pulmonary emboli.

There was no significant disease in the other major organ systems.

This case illustrates the process of subendocardial or zonal infarction of the myocardium, as distinct from regional infarc-



Fig. 4. Aortic valve showing marked thickening, deformity and stenosis.



Fig. 5. Microscopic appearance of the infarction. Note subendocardial localization, vacuolated appearance of affected muscle cells, and lack of inflammatory infiltrate.

tion in which the heart muscle in a region supplied by a particular branch of the coronary arteries is affected. This localization is uncommon; it was found in 10 per cent of a series of 65 myocardial infarcts studied by Levine and Ford.[4] Dr. Lage has described how, under conditions of increased intraventricular pressure, relatively less coronary blood flow may be expected in subendocardial regions as a result of decreasing pressure within the terminal branches of the coronary arteries, combined with relatively greater pressure in this zone of the myocardium as a result of ventricular contraction.[5] The subendocardial region may thus be predisposed to relative anoxia with consequent myocardial damage when total coronary blood flow has been reduced as a result of arteriosclerosis or aortic stenosis. Fulton[6] offers the additional explanation based on experimental studies that, as a consequence of prolonged ischemia of the inner zone of myocardium, an extensive system of anastomoses develops and any sudden reduction of coronary blood flow may cause infarction throughout the entire zone supplied by this system, rather than in a region supplied by a single branch of a coronary artery.

The etiology of the pericarditis and its relationship to the myocardial process are not clear. Pericarditis is of course a frequent occurrence in myocardial infarction,[7] and is thought to represent inflammatory reaction to products of myocardial necrosis. It reflects infarction of the heart muscle directly underlying the pericardium,[7] although the area of pericarditis may not be confined to the infarcted region. In the present case, however, no evidence could be found of extension of the infarction to the outer one-half of the myocardium. Besides this, the extent of organization of the pericardial exudates suggests a duration of the pericarditis of 10 to 14 days, while it is doubtful that the acute infarction was older than a week. The pericardial reaction was nonspecific and contained no tissue alterations indicative of rheumatic origin. It is at least possible that the pericarditis was idiopathic and may have precipitated the acute episode, rather than resulting from the infarction.

ANATOMICAL DIAGNOSES. *Aortic stenosis, cardiac hypertrophy predominately left ventricular, acute subendocardial (zonal) infarction of myocardium, fibrinous pericarditis, pleural effusions, and chronic passive congestion of lungs.*

REFERENCES

1. Contratto, A. W., and Levine, S. A.: Aortic stenosis with a special reference to angina pectoris and syncope, Ann. Intern. Med. 10:1636, 1937.
2. Schlesinger, M. J., and Reiner, L.: Focal myocytolysis of the heart, Amer. J. Path. 31:443, 1955.
3. Hudson, R. E. B.: Cardiovascular pathology, Vol. 1, Baltimore, 1965, The Williams & Wilkins Company, pp. 647-656.
4. Levine, H. D., and Ford, R. V.: Subendocardial infarction: report of 6 cases and critical survey of the literature, Circulation 1:234, 1939.
5. Johnson, J. R., and DiPalma, J. R.: Intramyocardial pressure and its relation to aortic blood pressure, Amer. J. Physiol. 125:234, 1939.
6. Fulton, W. F. M.: Chronic generalized myocardial ischaemia with advanced coronary artery disease, Brit. Heart J. 18:341, 1956.
7. Spodick, D. H.: Acute pericarditis, New York, 1959, Grune & Stratton, Inc., p. 125.

Relationship of extracellular fluid volume to the development of drug resistance in the hypertensive patient

Frank A. Finnerly, Jr., M.D.
Washington, D. C.

Several investigators have demonstrated that the chronic administration of many antihypertensive agents is frequently associated with sodium retention.[1-4] Reports from this laboratory have particularly emphasized the sodium-retaining properties of intravenous diazoxide[1,5] and orally administered clonidine. The chronic administration of both these agents has frequently been associated with weight gain and a progressive rise in the arterial pressure which could not be controlled by increasing the dose to toxic levels. The addition of diuretics to the regimen was promptly followed by weight loss in some and a decrease in arterial pressure and re-establishment of sensitivity to antihypertensive agents in all.

The finding that the fall in arterial pressure during drug induced diuresis was due mainly to a decrease in extracellular fluid (ECF) volume[9] suggested the possibility that an expanded ECF volume might contribute to the development of apparent drug resistance. In order to verify this relationship serial determinations of extracellular fluid volume and arterial pressure were measured in a group of 14 patients who were receiving antihypertensive agents without diuretics. None of these patients was in congestive heart failure and none was uremic. Four patients received daily injections of 300 mg. of diazoxide intravenously whereas 10 patients received oral medication: 5 of these received methyldopa and 5 received hydralazine. The aim of therapy in these patients was to maintain the diastolic pressure under 110 mm. Hg in the sitting position. Resistance was defined as the persistence of the diastolic blood pressure above 130 mm. Hg for two successive days despite full doses of therapy.

During the first three days of diazoxide therapy there was a 35 per cent average reduction in mean arterial pressure which lasted an average of 10 hours. By the tenth day 300 mg. of diazoxide produced only a 6 per cent average reduction in mean arterial pressure which lasted for less than one hour. Although there was a 6.8 pound average weight gain in the 10 diazoxide-treated patients there was no significant increase in central venous pressure. There had been a 3.27 liter average increase in ECF volume and a 549 ml. average increase in plasma volume. Administration of 80 mg. of furosemide produced a 45 per cent average decrease in mean arterial pressure, a 3.4 liter average decrease in ECF volume, and a 462 ml. average decrease in plasma volume.

By the end of the first month of therapy

From the Department of Medicine, Georgetown University School of Medicine and the Georgetown University Medical Division, District of Columbia General Hospital, Washington, D. C.

tion in which the heart muscle in a region supplied by a particular branch of the coronary arteries is affected This localization is uncommon it was found in 10 per cent of a series of 65 myocardial infarcts studied by Levine and Ford[4] Dr Lage has described how under conditions of increased intraventricular pressure relatively less coronary blood flow may be expected in subendocardial regions as a result of decreasing pressure within the terminal branches of the coronary arteries combined with relatively greater pressure in this zone of the myocardium as a result of ventricular contraction[5] The subendocardial region may thus be predisposed to relative anoxia with consequent myocardial damage when total coronary blood flow has been reduced as a result of arteriosclerosis or aortic stenosis. Fulton[6] offers the additional explanation based on experimental studies that as a consequence of prolonged ischemia of the inner zone of myocardium an extensive system of anastomoses develops and any sudden reduction of coronary blood flow may cause infarction throughout the entire zone supplied by this system rather than in a region supplied by a single branch of a coronary artery

The etiology of the pericarditis and its relationship to the myocardial process are not clear Pericarditis is of course a frequent occurrence in myocardial infarction[7] and is thought to represent inflammatory reaction to products of myocardial necrosis It reflects infarction of the heart muscle directly underlying the pericardium[7] although the area of pericarditis may not be confined to the infarcted region In the present case however no evidence could be found of extension of the infarction to the outer one-half of the myocardium. Besides this, the extent of organization of the pericardial exudates suggests a duration of the pericarditis of 10 to 14 days, while it is doubtful that the acute infarction was older than a week. The pericardial reaction was nonspecific and contained no tissue alterations indicative of rheumatic origin It is at least possible that the pericarditis was idiopathic and may have precipitated the acute episode rather than resulting from the infarction

ANATOMICAL DIAGNOSES *Aortic stenosis, cardiac hypertrophy predominately left ventricular acute subendocardial (zonal) infarction of myocardium fibrinous pericarditis pleural effusions and chronic passive congestion of lungs*

REFERENCES

1 Contratto, A. W and Levine, S. A. Aortic stenosis with a special reference to angina pectoris and syncope, Ann. Intern. Med. 10:1636, 1937
2 Schlesinger M J and Reiner L.: Focal myocytolysis of the heart, Amer J Path. 31:443, 1955
3 Hudson R E. B Cardiovascular pathology Vol. 1 Baltimore, 1965 The Williams & Wilkins Company pp. 647 656
4. Levine, H D and Ford R. V Subendocardial infarction report of 6 cases and critical survey of the literature, Circulation 1:234 1939
5 Johnson, J R. and DiPalma, J R. Intramyocardial pressure and its relation to aortic blood pressure, Amer J Physiol. 125:234 1939
6. Fulton, W F M Chronic generalized myocardial ischaemia with advanced coronary artery disease, Brit. Heart J 18:341 1956.
7 Spodick, D H Acute pericarditis, New York, 1959 Grune & Stratton, Inc., p. 125.

ing the dose of thiazide diuretics (if the patient is receiving thiazides) does not lower the arterial pressure increase diuresis, or alter the ECF volume. The potency of thiazide diuretics cannot be increased by increasing the dose, e.g. 4 Gm. of chlorothiazide a day exerts no more diuresis than 1 Gm. Only since the availability of the loop diuretics, furosemide and ethacrynic acid, has it been possible to contract an expanded ECF volume in patients who are already receiving diuretics. These agents are particularly useful in this regard not only because they are 30 to 35 times more potent than the thiazides, but also because their potency can be significantly increased by increasing the dosage.

During the past year we have found the addition of furosemide (in that dosage sufficient to produce diuresis and maintain dry weight) the most valuable adjunct to the therapy of the resistant hypertensive patient. In such patients who are receiving full doses of antihypertensive agents and thiazide diuretics, 80 to 160 mg. of furosemide administered daily or every other day has promptly produced diuresis and restored the sensitivity to antihypertensive agents. In our experience the hypertensive patient should not be considered resistant until his ECF has been contracted by loop diuretics. Not only has the sensitivity to antihypertensive agents been restored but in 18 of the 20 patients so treated it has been possible to maintain the arterial pressure under good control using only half the dosage of the antihypertensive agents.

REFERENCES

1. Muelheims, G. H., and Brown, G. D., Jr.: Effect of guanethidine therapy on total blood volume in patients with essential hypertension, Proc. Soc. Exp. Biol. Med. 109:613, 1962.
2. Dollery, C. T., and Harington, M.: Methyldopa in hypertension. Clinical and pharmacological studies, Lancet 1:759, 1962.
3. Bayliss, R. I. S., and Harvey-Smith, E. A.: Methyldopa in the treatment of hypertension, Lancet 1:763, 1962.
4. Smith, A. J.: Fluid retention produced by guanethidine, Circulation 31:490, 1965.
5. Gill, J. R., Mason, D. T., and Bartter, F. C.: Adrenergic nervous system in sodium metabolism. Effects of guanethidine and sodium retaining steroids in normal man, J. Clin. Invest. 43:177, 1964.
6. Roonov Jensen, V., and Hansen, J.: Blood volume and exchangeable sodium during treatment of hypertension with guanethidine and hydrochlorothiazide, Acta Med. Scand. 186:255, 1969.
7. Flanerty, F. A., Jr., Kakaviatos, N., Tuckman, J., and Magill, J.: Clinical evaluation of diazoxide, new treatment for acute hypertension, Circulation 28:203, 1963.
8. Mroczek, W. J., Davidov, M., Gavrilovich, L., and Finnerty, F. A., Jr.: The value of aggressive therapy in the hypertensive patient with azotemia, Circulation 40:893, 1970.
9. Davidov, M., Kakaviatos, N., and Finnerty, F. A., Jr.: The antihypertensive effects of an imidazoline compound, Clin. Pharmacol. Ther. 8:810, 1967.
10. Davidov, M., Gavrilovich, L., Mroczek, W., and Finnerty, F. A., Jr.: Relation of extracellular fluid volume to arterial pressure during drug-induced saluresis, Circulation 40:349, 1969.
11. Finnerty, F. A., Jr., Mroczek, W., Davidov, M., and Gavrilovich, L.: The influence of extracellular fluid volume on antihypertensive drug response, Circ. Res. In press.

the diastolic pressure in each of the 10 patients receiving methyldopa or hydrala zine was under 110 mm Hg At this time there was no significant change in the ECF volume Between the ninth and eleventh weeks the diastolic pressure in 5 of these patients was consistently over 130 The other five patients remained under good control In the 5 patients who had de veloped apparent drug resistance there had been an 1 86 liter average increase in ECF and a 446 ml average increase in plasma volume whereas in the 5 patients whose arterial pressure remained under good control the ECF and the plasma volume had not significantly changed There had been no significant change in central venous pressure in any of these patients Administration of diuretics in the 5 patients with high diastolic pressure produced a 42 per cent average fall in mean arterial pressure a 2 6 liter average reduction in ECF and a 5?2 ml average fall in plasma volume

The observation that the ECF was elevated in 9 of the patients and was not elevated in the other 5 suggests that the expansion of the ECF was largely responsible for the apparent drug resistance The decrease in ECF volume the lowering of the arterial pressure and the re-establishment of sensitivity to antihyper tensive agents following diuretics further supports this explanation

That an expanded ECF volume can rapidly decrease antihypertensive activity can readily be documented by comparing the fall in arterial pressure before and after infusions of glucose and water Nine patients received intravenous injec tions of 300 mg of diazoxide 5 patients received intramuscular injections of 20 mg of hydralazine and 4 patients received intramuscular injections of 2 5 mg of reserpine. Before glucose there was a 23 per cent average reduction in mean arterial pressure whereas following glucose the same dosage of antihypertensive agents produced only a 6 per cent average reduc tion in mean arterial pressure. There was no significant change in either the cardiac output or central venous pressure. These data help to explain the poor response to antihypertensive agents in patients with congestive heart failure and also may account for the variability in drug response following the parenteral administration of a particular agent not only from patient to patient but in the same patient at different times. Thus diazoxide administered intravenously to a patient with hypertensive encephalopathy was followed by only a 6 per cent fall in mean arterial pressure lasting for half an hour Pretreating this patient with furosemide the following day and repeating the diazoxide in the same dosage produced a 23 per cent fall mean arterial pressure lasting for half an hour Pretreating this patient with furosemide the following day and repeat ing the diazoxide in the same dosage produced a 23 per cent fall in mean arterial pressure which lasted for 12 hours.

Clinical experience attests to the fact that drug resistance develops more commonly in patients receiving antihyperten sive agents alone than in patients receiving antihypertensive agents in conjunction with diuretics. It would seem from the data presented that the concomitant ad ministration of diuretics decreases sodium retention and thereby prevents the expan sion of ECF and the ultimate development of drug resistance. It is interesting to speculate further in this regard whether the enhanced therapeutic response observed when diuretics are added to an antihypertensive regimen represents true synergism of action or simply a decrease in ECF volume Since an expanded extra cellular fluid seems to decrease antihyper tensive activity and in some patients contributes to the development of drug resistance and since diuretics decrease extracellular fluid and can frequently reverse or prevent these phenomena it would seem that diuretics should be an integral part of all antihypertensive regi mens parenteral as well as oral

Finally these data would suggest that the primary approach to the treatment of the resistant hypertensive patient should be reduction of ECF volume. Increasing the dose of antihypertensive agents in the presence of an expanded ECF volume has no effect on the arterial pressure (even though the toxic effects may be increased) It should also be emphasized that increas-

the shortcomings of morphine as an ideal analgesic. However among its advantages, it will relieve the pain and distress of acute myocardial infarction and induce sleep. The sedation and the beneficial effect on the incipient or overt left ventricular failure will all help to reduce purposeless muscular activity and the work of the heart. Among its disadvantages, the drug may afflict an already seriously ill patient with distressing nausea and vomiting and there is no way of predicting this. This effect may be avoided, to some extent, by combining the morphine with an antiemetic such as cyclizine.

Morphine exerts its analgesic action not only by increasing the pain threshold, i.e., *the magnitude of the stimulus necessary* to evoke pain but also, by dulling the reaction to pain, it has the capacity to alter the reaction to pain. Morphine also reduces the sympathoadrenal response to painful stimuli thereby further alleviating the reaction to pain. Suggestibility is an important factor not only in the degree to which pain emerges under a given condition, but also in the response to drug therapy. A physician who is understanding of this aspect of his patient's management will secure the most advantage from the administration of the analgesic.

The route of administration of the drug determines its time of onset of action. For example, with intravenously administered morphine, the analgesic effect is almost immediate and reaches its peak in 20 minutes. After intramuscular or subcutaneous administration peak activity is only reached at 45 to 90 minutes. This delay in onset was well recognized many years ago. Sir James MacKenzie, writing in his classic, *Diseases of the heart*, in 1925 stated "When the pain is of an agonizing nature and the morphine is long in taking effect, chloroform may be required to produce unconsciousness for 5 or 10 minutes until the morphine has time to act."

The fate of morphine is primarily dependent upon biotransformation in the liver. Although the narcotic effect is over 4 to 6 hours, only 50 per cent is detoxified in the first 24 hours and it is 36 hours after injection that 90 per cent will have been eliminated. The end products are excreted through the kidneys. Because of its detoxification in the liver one may expect that in hepatic insufficiency the action will be prolonged and cumulative effects will be likely. The biotransformation of morphine is largely dependent on conjugation with glucuronic acid, the synthesis of which is impaired quite early in the course of hepatic disease.

One of the earliest reports of the use of intravenous morphine in acute myocardial infarction was in 1930 by Moor who described a patient who failed to respond to the hypodermic injection of morphine but responded dramatically when the drug was administered intravenously. Moor went on to say "I do not know whether the intravenous method of giving morphine is altogether safe but it was certainly most effective in this case."[7] Today we are aware that *administration of morphine is not without* risk in patients with myocardial infarction and it is now in this direction that we shall turn our attention.

Thomas and associates[12] in a study of the hemodynamic effects of morphine in patients with acute myocardial infarction have shown that individuals respond very differently—the blood pressure fell transiently in half the patients and occasionally morphine precipitated a dramatic fall. The maximum dose administered was 10 mg given at a rate of 1.0 mg per minute. It should be noted that this dose is often exceeded therapeutically. The hypotension is due to venous pooling and a bradycardia secondary to a vagomimetic effect. Consequently elevation of the lower extremities may quickly restore the blood pressure. They suggested that intravenous administration *may be preferable to the intra*muscular route, as the hypotensive phase would occur while the doctor was with the patient *and able to* take appropriate action. It also meant that the injection could be given slowly and stopped at the smallest dose producing the desired effect. It is interesting to note the findings of Lowenstein and co-workers in a recent study of the cardiovascular responses to large doses of intravenous morphine 1.0 mg per kilogram. They showed that the drug had minimal effects on the cardiovascular system of supine intact man without clinically

The role of morphine in acute myocardial infarction

David Todres M D F F A R C S*
Bronx N Y

Knowledge comes but wisdom lingers—Tennyson

Thomas Sydenham the 17th century English physician wrote Among the remedies which it has pleased Almighty God to give man to relieve his sufferings none is so universal and so efficacious as opium Three hundred years later morphine is still probably the most beneficial analgesic in acute myocardial infarction and despite reports of its adverse effects it seems likely to retain its important place in the management of this distressing condition Today we are equipped with a greater knowledge of the disease and the drug than we were at the time Voltaire exclaimed that medical treatment consisted in pouring drugs of which we knew nothing into a patient of whom we knew less.

A review of our knowledge of morphine s properties and particularly the studies over the past decade of the effect of morphine (and related narcotics) in acute myocardial infarction is helpful in evaluating its proper place today Opium is obtained from the opium poppy (*Papaver somniferum*) by scarrifying the unripe seed capsule and collecting and drying the exudate The substance is a mixture of at least 20 alkaloids about 10 per cent of which is morphine Morphine was first isolated in 1805 by Frederick Serturner an Apothecary s assistant in Paderborn Germany It was, however another 120 years before the structure was identified by Gulland and Robinson

Analgesic activity depends quite specifically on molecular geometry The morphine molecule is levorotatory There is no mirror image of the drug in nature but a synthesized dextrorotatory counterpart that possesses none of morphine s properties. Addiction liability seems to parallel analgesic activity and this has been found to apply to related compounds of morphine in spite of initial statements to the contrary Thus the search for ideal analgesia continues. Grollman has described the features of the ideal analgesic as follows It should obliterate pain and diminish the anxiety associated with it, while exerting a minimal degree of narcosis and stupefaction It should be free of such undesirable side-effects as constipation nausea and respiratory depression and should have no tendency to addict or develop tolerance It should have a rapid onset and long duration should be effective and well tolerated when administered orally and relatively inexpensive [1] With this in mind we are immediately aware of

From Montefiore Hospital and Medical Center Bronx, N Y and Albert Einstein College of Medicine, Yeshiva University Bronx, N Y
*Director Medical Surgical Intensive Care Unit; Attending Anesthesiologist, Montefiore Hospital and Medical Center and Assistant Professor of Anesthesiology Albert Einstein College of Medicine, Yeshiva University

suggested that the use of intravenous pentazocine, particularly in a dose of 60 mg may be unsuitable after acute myocardial infarction

With increasing use of pentazocine, it is becoming more evident that the incidence and intensity of psychomimetic effects is greater than that of the narcotics. It has also been reported that pentazocine may have some addiction liability We must be alerted to the fact that there are risks in the administration of "safe analgesics" and that the physician is obligated to exercise caution at all times—*primum non nocere!*

Meperidine has also enjoyed a degree of popularity in the management of pain of acute myocardial infarction. Rees and co-workers,[8] however in a study of acute myocardial infarction administered 100 mg of meperidine intravenously They found a biphasic response consisting initially of a rise in mean systemic arterial pressure systemic vascular resistance and heart rate. This was followed in 10 to 15 minutes by a fall in these variables below those in the control period They concluded that the cardiovascular effects of the drug made it less than the ideal drug for the relief of pain in myocardial infarction.

In choosing an alternative to morphine it is often claimed that the newer analgesic is less depressant to the respiratory system Most studies, however have found that when equianalgesic doses are used the degree of respiratory depression observed is not significantly different from that seen with morphine. In fact some workers have stated that in equianalgesic doses, meperidine produces almost twice as much respiratory depression as morphine! The respiratory depression caused by narcotics is potentiated by sleep, advanced age pulmonary and liver diseases, and hypothyroidism Alcohol barbiturates, and monoamine oxidase inhibitors increase the respiratory depressant effect of narcotics. Morphine should be used with great caution in patients with cor pulmonale, since deaths following ordinary therapeutic doses have been reported. Caution in its use is necessary in any situation in which there is decreased respiratory reserve including emphysema, kyphoscoliosis, and even severe obesity

Many physicians prefer diamorphine (heroin) 5 to 10 mg intramuscularly as a pain reliever particularly if morphine fails to bring complete relief Vomiting and hypotension are said to be less likely and the pain killing powers greater The medical use of diamorphine is not illegal in the United Kingdom

Arterial hypoxemia in myocardial infarction has been documented in a number of studies now Both acidosis (particularly in pulmonary edema) and alkalosis have been reported. Shunting is a significant contributor to hypoxemia. The shunting includes passage of blood through alveoli which are essentially unventilated through anatomic shunts, and through alveoli filled with edema fluid In many instances the deranged pulmonary function is at least partially reversible by deep breathing This would be a warning to the overzealous use of narcotics with the production of respiratory depression a reduction in pO_2, and the possible unfavorable effects on the already injured myocardium Morphine too by its depressant effect on respiration may cause an elevation of the pCO_2 and thus aggravate any existing acidosis with its undesirable effect on myocardial contractility

Increased urinary catecholamine excretion has been reported in many patients with acute myocardial infarction The association of catecholamine administration and serious ventricular arrhythmias is widely recognized in both clinical and experimental studies. Sedation with morphine through reduction in catecholamine output, may play a part in diminishing the incidence of ventricular arrhythmias.

To relieve pain and suffering is one of the physician's noblest actions. It would be a great thing to understand pain in all its meaning as Latham once remarked but with our limited understanding of things we hope we have acquired the necessary wisdom to serve our fellow human beings in the best possible way Sir James MacKenzie, writing in 1923 said In giving a remedy even although we have faith in it, we must always do it with a mind watchful and critical recognizing that if this remedy fails one must seek for some other that would be more effective.

diagnosed heart disease. In the presence of symptomatic aortic valve disease the hemodynamic response to the drug was altered These patients demonstrated a significant rise in cardiac index and stroke index a decrease in systemic vascular resistance and a rise in pulmonary artery and central venous pressures.

Drew and Dripps[10] showed that 44 per cent of the subjects who had been given 12 to 20 mg of morphine had severe hypotension when put in an upright position on a tilted table This reminder of the serious hypotension which may follow the administration of morphine when the patient is not supine is necessary when considering the transport of patients with acute myocardial infarction to the hospital namely that they should not be carried in a leg down position as this may lead to a severe fall in blood pressure with possible disastrous effects Morphine and other narcotics should be used with caution in patients who have a decreased blood volume since they are prone to develop hypotension The concurrent use of a narcotic analgesic with a phenothiazine derivative not only augments the respiratory depression produced by the narcotic but also results in a greatly increased risk of hypotension

Response to intravenous morphine in acute left ventricular failure and pulmonary edema is dramatic Morphine produces a decrease in venous tone and peripheral pooling of blood The pooling of blood is a factor in the relief of pulmonary edema but probably the major factor is a sustained reduction in cardiac output and a decrease in left ventricular minute work In addition the drug produces an alteration of the patient s reaction to impaired respiratory function and an indirect reduction of the work of the heart due to reduced fear and apprehension

Morphine depresses the respiratory centers directly There is some respiratory depression even with doses too small to produce sleep or disturb consciousness. The degree of depression is proportional to the dose and in fact, an overdose which is fatal is due to the profound respiratory depression which occurs. There is a depression of both rate and tidal volume. Respiratory depression is characterized by slow irregular periodic respiration Maximal respiratory depression occurs within approximately 7 minutes after intravenous morphine but may not be seen for as long as 30 minutes after intramuscular administration or as long as 90 minutes after subcutaneous administration

The mechanism of respiratory depression is a decreased responsiveness of the brain stem respiratory centers to increase in pCO_2 After large doses of morphine patients will breathe if instructed to do so, but without such instruction they may remain relatively apneic Natural sleep also produces a decrease in the sensitivity of the respiratory center to CO_2 and the effects of morphine and sleep are additive.

Recognizing the adverse effects that may be produced by the administration of morphine investigators have searched for newer and safer analgesic agents in the management of acute myocardial infarction Lal and associates[11] have reported on the cardiovascular and respiratory effects of morphine and pentazocine (Talwin) and concluded that pentazocine seemed preferable to morphine being associated with an increase in blood pressure and a decrease in VD/VT (dead space tidal volume) ratio and the alveolar arterial oxygen gradient. Administration of morphine however was associated with an increase in VD/VT ratio and alveolar arterial oxygen gradient. Pentazocine is a narcotic antagonist which possesses comparable analgesic potency to heroin methadone and morphine when given to patients with myocardial infarction However with severe pain some workers have concluded that it is less effective than morphine With an increase in the dose of pentazocine above the usual therapeutic dose one does not get more analgesia only more respiratory depression

Jewitt and co-workers[12] however found that 30 to 60 mg of pentazocine given intravenously to patients with acute myocardial infarction resulted in a rise in mean pulmonary artery pressure. Central aortic pressure rose at the same time, and this change provided an after load stress to the heart by increasing the resistance to left ventricular ejection An increase in left ventricular work was present 20 minutes after giving 60 mg of pentazocine The results

Annotations

Angina or no angina: What difference does it make?

The clinical cardiologist is frequently presented with the sometimes perplexing problem "Does my patient have angina or doesn't he?" Although a few well-chosen questions and an electrocardiogram are, in perhaps the majority of all cases, all that are required to solve this dilemma, more complicated procedures, including exercise-stress testing and even angiocardiography, are more and more commonly being utilized for purposes of providing a "definite" diagnosis.

This diagnosis then serves to place all patients into one of two possible categories, each with its own therapeutic pattern. Those with coronary artery disease are usually advised to curtail cigarette smoking, control their weight, limit their intake of saturated fats, initiate proper exercise habits, and attempt to control their environmental and personal stress. Where appropriate, they may also be placed on drug therapy for hypertension, hyperglycemia, hyperuricemia, and the symptomatic relief of chest pain.

In the case of the patient in whom coronary artery disease cannot be documented regardless of the extent to which diagnostic testing is carried out, the advice given the patient is quite different. He is informed that his "heart" is perfectly normal and that his chest pain is due to some other cause. As a rule, the physician can rationally attribute the pain to another organic condition. Frequently there is an incidental hiatus hernia to which the patient's symptoms can be ascribed. Often, there is localized chest wall tenderness, gastritis, some form of pulmonary consolidation on chest x-ray, suggestion of pericarditis, or a wide variety of other possible organic conditions which could conceivably be responsible for the chest pain. In only a minority of such cases must the physician frankly indicate to the patient that he can define no organic disease, however, relegating the complaint to the level of psychophysiologic or psychosomatic illness.

In any event, the patient in whom coronary heart disease cannot be documented is reassured, told that there is no reason for concern, and frequently sent home on some form of sedative or tranquilizer. The cardiologist himself feels confident that he has ruled out a potentially serious disease in a patient who was quite concerned about his health. A definite service has been performed and a job has been well-done.

Yet, the spectrum of coronary heart disease covers a broad range of anatomic, biochemical, physiologic, clinical, and pathological variants. It is often surprising how severe a degree of coronary atherosclerosis can be found on autopsy in patients who never complained of clinical angina. By the same token, it has now been well-documented that a fair percentage of patients who experience chest pain which is in all respects typical of *angina actually have* normal coronary vessels on angiographic evaluation.

Block and associates[1] have reported that the prognosis for patients with angina is, statistically at least, not a favorable one and mean life expectancy following initial diagnosis is only about six years. Despite recent advances in the symptomatic treatment of anginal pain by diverse medical and surgical means, therapeutic intervention appears to have had little, if any, measurable effect upon life expectancy in patients with this condition. Any objective benefit can, at least in part, be explained by the earlier detection of coronary heart disease in mildly symptomatic individuals by means of the fairly widespread use of two-step, bicycle, or even treadmill exercise-testing procedures. This artificial increase in life expectancy through broadening of diagnostic criteria should not be interpreted as implying more successful therapeutic intervention.

In fact, it is unrealistic to assume that medical therapy,* short of reversing the atherosclerotic (or aging?) process, will ever be particularly successful in the treatment of coronary artery disease. By the time clinical angina has developed, the patient has already lost perhaps 80 per cent or more of the cross-sectional area of his coronary arteries. His pain exists despite the functioning of coronary collaterals, which by this time may already be highly developed. In attempting to treat his patient, the cardiologist must be mindful that the loss of an additional 10 per cent of arterial cross-sectional area may result in coronary flow which is inadequate to sustain life.

Yet, in the patient with chest pain in whom coronary disease cannot be documented there is much to suggest that the physician can be fairly successful in preventing, or at least retarding, the development of significant coronary artery disease. It has previously been mentioned that the patient with a diagnosis of coronary disease is usually provided with certain advice regarding smoking, weight con-

*It is possible that this discussion might not apply to present or future surgical therapy.

REFERENCES

1. Goodman, L. S. and Gilman, A.: The pharmacological basis of therapeutics, ed 4 New York, 1970 The Macmillan Company
2. Crollman, A. Use of drugs in relief of pain in Finneson, B E. editor Diagnosi and management of pain syndromes Philadelphia, 1969 W B Saunders Company p 33
3. Foldes F F Swerdlow M and Siker E. S Narcotics and narcotic antagonists, Springfield Ill 1964 Charles C Thomas Publisher
4. Mackenzie Sir James Angina pectoris, Oxford England 1923 Oxford Medical Publication.
5. Mackenzie, Sir James Diseases of the heart ed 4 Oxford England 19.5 Oxford Medical Publication.
6. Leading article Pain relief in acute myocardial infarct on, Brit. Med J 2:3 1966.
7. Moor F Intravenou use of morphine in acute myocardial infarction Lancet .1 :959 1930
8. Eckenhoff J E. and Oech S. R. The effects of narcotics and antagoni ts upon respiration and circulation in man Clin. Pharmacol. Therap. 1:183 1960
9. Lowenstein E., et al. Cardiovascular response to large doses of intravenous morphine in man, New Eng J Med. 281:1389 1969
10. Drew J H and Dripps, J H Jr Clinical studies of morphine II Anesthesiology 7:44 1946.
11. Lal S. Savidge, R. S., and Davies, D M: Analgesics in myocardial infarction, Amer. Heart J 9:717 1970.
12. Thomas, M., et al. Hemodynamic effects of morphine in patients with acute myocardial infarction, Brit. Heart J 27:863 1965.
13. Jewitt, D E. et al. Increased pulmonary artery pressure after pentazocine in myocardial infarction, Brit. Med. J 1:795, 19 0.
14. Scott M E., and Orr R. Effects of diamorphine, methadone, morphine and pentazocine in patients with suspected myocardial infarction, Lancet 1:1065 1969
15. Rees, H A., et al. Circulatory effects of pethidine in patients with acute myocardial infarction, Lancet 2:863 1967

of the Voigt form of the three-element model to Sonnenblick original data[1] indicates that 25 per cent increase of fiber length results in 50 per cent increase of CE V_{max}. Application of the Maxwell model—thought more likely by some—results in 70 per cent shift of CE V_{max} for 25 per cent change of fiber length. Application of four element models ould be expected to result in dependence of CE V_{max} upon fiber length intermediat between the Voigt and Max ell models. Therefore, unlike V_{max} of the hole muscle, CE V_{max} does depend on the alue of end-diastolic fiber length, at least according t current concepts.

Moreover there is reason t doubt the generality of the original observation that even whole muscle V_{max} is independent of fiber length. Although whole muscle V_{max} was show to be independent of fiber length under specific set of experimental conditions —i afterloaded isotonic contraction t 23° C.— there is evidence that such independence does not hold under other experimental circumstances Noble and associates, using quick-release technique, found that hole muscle V_{max} as not independent of fiber length, but rather shared the same sensitivity to fiber length as maximum isometric force.

It is not difficult to see how the particular circumstances in the afterloaded isotonic experiments under hich hole muscle V_{max} was obtained ha influenced the unusual results, i.e., the independence of V_{max} from fiber length. Unlike skeletal muscle, the activ state in cardiac muscle has been found to be slow in onset and transient in nature That is, t rises in early systole toward maximum value and then declines toward zero at end systole. Thus the force-velocity relations in cardiac muscle cannot be thought of as tatic, but rather must be thought of as shifting upward ith time early i the contractile cycle and then back dow t the end of the contractile cycle For this reason, it is essential that any conclusions dra regarding the dependence or independence of V_{max} from fiber length be made on the basis of data taken at precisely equivalent instants in the contractile cycle otherwise the issue is confused by arying influence of the level of activ state on the force-velocity curves. The quick release force elocity curves, hich show marked dependence of hole muscle V_{max} on fiber length, are measured at the same level of active state The afterloaded isotonic force-velocity curves, on the other hand, hich result in no dependence of muscle V_{max} on fiber length, are measured t varying levels of active state. I fact, the activ tate levels for these measurements vary from zero to 100 per cent!

If afterloaded isotonic data are corrected to equivalent levels of activ state[5] the fiber length independence of whole muscle V_{max} proves ... to dependence not unlike that measured by quick release methods. It is therefore concluded that the fiber length independence of whole muscle V_{max} reported in afterloaded isotonic experiments is in part fortuitous result of the particular experimental protocol, rather than general property of cardiac muscle.

I conclusion, the validity of the use of CE V_{max} as contractile index is challenged on the basis that (1) except under special experimental conditions, muscle V_{max}—from which CE V_{max} is calculated—appears to be dependent pon fiber length (2) calculation show that CE V_{max} is even more highly dependent pon fiber length than whole muscle V_{max} (3) the relatively high sensitivity of CE V_{max} to fiber length means that shifts of CE V_{max} induced by changes in fiber length cannot be distinguished from inotropically induced shifts of CE V_{max}. Thus upward shift of CE V_{max} cannot be unequivocally attributed to an increase of muscle contractility

These arguments, spelled out in greater detail in reference 5 suggest that basic uncertainties place limitations on the ultimate value of the V_{max} technique.

Gerald H Pollack, Ph.D
Anesthesia Research Center and
Center for Bioengineering
University of Washington
Seattle Wash. 98105

REFERENCES

1. Sonnenblick, E. H. Force elocity relations in mammalian heart muscle, Amer J Physiol. 202:931 1962.
2. Hefner L. L., and Bowen, T E J Elastic components of cat papillary muscle, Amer J Physiol 212 1221 1967
3. Brady A. J Three element model of muscle mechanics: Its applicability to cardiac muscle, Physiologist 10:75, 1967
4. Parmley W W and Sonnenblick, E. H. Series elasticity in heart muscle: Its relation to contractile element elocity and proposed muscle models, Circ Res. 20:112, 1967
5. Pollack, G. H. Maximum velocity as an index of contractility in cardiac muscle, Circ. Res. 26 111, 1970.
6. Noble, M I M, Bowen, T E., and Hefner L. L.: Force elocity relations of cat cardiac muscle, studied by isotonic and quick release techniques, Circ. Res. 24:821 1969

An elegant transplant

Gurdon[1-4] of the Department of Zoology of Oxford University has been conducting outstanding studies in transplantation. For example, he and his associates ha successfully transplanted the nucleus of mature intestinal cell of frog (Xenopus laevis) into the enucleated ovum of another frog with the result that the ovum developed into fertile adult frog. Among the developing embryos which followed

trol, diet exercise and the regulation of stress, as well as recommendations with regard to drug therapy for hypertension hyperglycemia hyperuricemia and the symptomatic relief of chest pain If such measures are to be helpful in the patient having late stage coronary disease it would also seem likely that they might produce beneficial results in the patient with marginal disease As a preventive measure one could argue as well for their adoption by the moderate-to-high-risk adult American male in whom there is probably a better than 50 per cent chance of developing either probable or suspect coronary disease by age 60.[6] In fact there is not insignificant evidence that the cardiologist can do substantially more to augment health and life among his patients by "treating" this latter group of "well" individuals than by caring only for those having demonstrable disease It is believed to be poor medical practice for the physician to "reassure" such patients without placing them on suitable preventive programs. This practice should be further condemned on the basis that many patients without typical pain patterns and/or demonstrable electrocardiographic changes will actually have subclinical coronary disease

The present thesis holds that for the patient without angina or with questionable angina or angina of mild to-moderate severity there should be no essential difference in basic medical therapy.[7] Because of the possibility of long term prevention of coronary artery disease the physician who fails to treat in the absence of demonstrable disease probably does a disservice to his patients. Whatever the difference in diagnostic or prognostic implications of angina versus no angina, the physician's basic therapeutic approach to these two groups of patients should, for all practical purposes, be identical

Philip I Hershberg, M.D
Department of Physiology
Harvard School of Public Health
Boston Mass.

REFERENCES

1 Lipberger H. V Klingeman, J D and Cosma, J Computer evaluation of statistical properties of clinical information in the differential diagnosis of chest pain Meth. Inform. Med. 7:79 1968.
2. Kemp, H G. Elliott W C., and Gorlin, R. The anginal syndrome with normal coronary arteriography Trans. Ass. Amer Physicians 80:59 1967
3 Block W J Jr Crumpacker E. L., Dry T J and Gage R. I Prognosis in angina pectoris—Observation in 6,882 cases, J A.M.A. 150:259 1952
4 Astrand I Kylin B and Lidstrom, I. M.: Electrocardiograms and exercise test in a health check, Scand J Clin. Lab. Invest. 23:31 1969
5 Wiggers, C. J The functional importance of coronary collaterals, Circulation 5:609 1952.
6. Epstein F H Ostrander L. D Jr Johnson, B C. et al. Epidemiological studies of cardiovascular disease in a total community—Tecumseh Michigan Ann. Intern. Med. 62:1170, 1965.
7 Stamler J Lectures on preventive cardiology New York, 1967 Grune & Stratton, Inc.

Is V_{max} a valid contractile index?*

Since the concept was introduced into the field of cardiac muscle mechanics, V_{max} has become increasingly popular as an index of contractility in both isolated muscle strips and the intact heart Despite widespread use there are theoretical arguments and experimental evidence which suggest that V_{max} is not a valid index of contractility

V_{max}, the intercept of the force-velocity curve with the velocity axis, was originally believed to satisfy the criteria for a contractile index (1) It was a characteristic of the contractile portion (contractile element) of the muscle (2) it was responsive to inotropic influences (3) it did not vary with end diastolic fiber length. It is items 1 and 3 to which exception is taken.

The original analysis of the data cited above[1] implicitly assumed that the two-element Hill model (contractile element in series with series elastic element) could be applied to cardiac muscle. Through such an assumption it was easy to demonstrate that measured V_{max} was identical to V_{max} of the contractile element (CE V_{max}) Thus since V_{max} of the muscle was found to be independent of fiber length it followed that CE V_{max} was also independent of fiber length apparently satisfying criteria 1 and 3

Since publication of that study almost a decade ago evidence has arisen from many laboratories that the two-element model valid for skeletal muscle at short lengths, does not apply to cardiac muscle. Rather it is now generally agreed that a minimum of three elements is required to represent cardiac muscle.[2-4] Some have even suggested four elements as the minimum

When three-element models are used instead of the original two-element model, conclusions different from those of Sonnenblick are reached. Application

*Supported by United States Public Health Service Grant GM 15991-02.

Fig. 1 Simultaneous endocardial and surface ECG. *A* Endocardial ECG as recorded from the bipolar catheter. As pacemaker fires there is sharp downward deflection (*P*) with rebound to the top of the graph. The transmitter is driven into saturation by the high-voltage discharge from pacemaker. The amplifier remains saturated and is therefore unable to display intracavitary events for about 0.12 sec., after which time there is gradual recovery. Endocardial QRS(E) does not inhibit the demand pacemaker; subsequent inappropriate discharge. QRS(E) is distorted by the recovering transmitter. *B* Surface Lead II does not demonstrate inappropriate firing of the demand pacemaker. *QRS* complexes 6 and 8 represent ventricular captures occurring close to the vulnerable period.

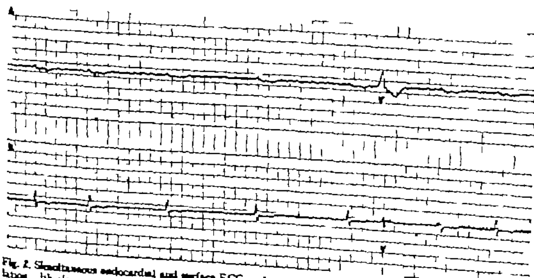


Fig. 2. Simultaneous endocardial and surface ECG with pacemaker off. *A*, Surface ECG showing atrial fibrillation with slow ventricular response and intraventricular conduction defect and low voltage and single PVC(V) of high amplitude. *B* Simultaneous endocardial ECG with pacemaker turned off shows PVC(V) of lower amplitude.

many such nuclear transplants were some with various anomalies. The incidence of fully developed fertile adults, embryos with anomalies and failures varied with the finesse of the technique. The technique not only is being improved but can be varied to vary the results desired.

These investigations are not only outstanding for genetics but for general cell and molecular biology. The nucleus of a differentiated cell (intestinal mucosa) placed in an ovum behaves like the nucleus of an undifferentiated gamete to produce ultimately all sorts of differentiated cells necessary for the production of a fertile adult frog. The possible and potential implications of these experiments in cell biology, molecular biology, genetics, and even organ transplantation are tremendous. Gurdon has shown that the cytoplasm of a cell is not merely passive in cell differentiation. The nature of the receptors in the cytoplasm is important in determining the response to messages from the nucleus and/or the nature of the messages which emanate from the nucleus.

As Gurdon[6] concludes, "These results show that a nucleus can promote the formation of a differentiated intestine cell and at the same time contain the genetic information necessary for the formation of all other types of differentiated somatic cell in a normal feeding tadpole. It is concluded that the differentiation of a cell cannot be dependent upon the incapacity of its nucleus to give rise to other types of differentiated cell."

The studies also show that the cytoplasm and other features of a cell determine to a large extent the function of and responses to the nucleus with its genetic material and other intrinsic functions.

G. E. Burch, M.D.
Tulane University School of Medicine
1430 Tulane Ave.
New Orleans, La. 70112

REFERENCES

1. Gurdon, J. B., and Uehlinger, V.: Fertile intestine nuclei, Nature 210:1240, 1966.
2. Elsdale, T. R., Gurdon, J. B., and Fischberg, M.: A description of the technique for nuclear transplantation in Xenopus laevis, J. Embryol. Exp. Morph. 8:437, 1960.
3. Gurdon, J. B.: Nuclear transplantation in amphibia and the importance of stable nuclear changes in promoting cellular differentiation, Quart. Rev. Biol. 38:54, 1963.
4. Fischberg, M., Gurdon, J. B., and Elsdale, T. R.: Nuclear transplantation in Xenopus laevis, Nature 181:424, 1958.
5. Gurdon, J. B.: The developmental capacity of nuclei taken from intestinal epithelium cells of feeding tadpoles, J. Embryol. Exp. Morph. 10:622, 1962.
6. Gurdon, J. B.: The developmental capacity of nuclei taken from differentiating endoderm cells of Xenopus laevis, J. Embryol. Exp. Morph. 8:505, 1960.

Pacemaker monitoring: Detection of pacemaker malfunction by use of simultaneous surface and endocardial leads

We are reporting a method for early detection of malfunction of temporary transvenous, ventricular inhibitory pacemakers. The method is based upon simultaneous recording of endocardial and surface electrocardiograms (ECG). In order to insure against leakage of current from line-operated equipment, the endocardial ECG was recorded by means of a battery powered telemetry unit (Gulton ECG telemetry system) from the pacemaker catheter (bipolar U. S. Catheter Instrument) which had been positioned under fluoroscopic control. The surface ECG was obtained from the bedside Coronary Care Unit monitor (American Optical). We studied three currently used temporary demand pacemakers (American Optical, Medtronic, and Cordis Chronocor II) which were battery operated and sensing from the endocardium; our findings follow:

1. As illustrated in Fig. 1, *B*, a surface ECG may be a poor index of adequate demand pacing, because it does not necessarily demonstrate the pacemaker spike (the latter is particularly small from a bipolar catheter electrode). What appear to be PVC's are actually pacemaker induced ventricular captures occurring near the vulnerable period. The simultaneous recording from the bipolar catheter clearly shows inappropriate pacemaker discharge spikes indicating pacemaker malfunction (in this instance due to lack of sensing because of poor endocardial contact). An endocardial lead (Fig. 1, *A*) per se may also be misleading, because pacemaker

Letters to the Editor

Effect of diphenylhydantoin on acetyl strophanthidin

To the Editor:

Some comments seem appropriate in regard to recent report published in the AMERICAN HEART JOURNAL (August, 1970) by Miller and Gilmore entitled "Influence of diphenylhydantoin on the inotropic and potassium-losing effects of acetyl strophanthidin." These authors state, "DPH has no influence on either the inotropic or potassium-losing effects of acetyl strophanthidin." They suggest that their findings differ from those of Scherlag and colleagues[1] and they paraphrase our conclusions that "DPH reverses the rise of coronary venous potassium concentration induced by acetyl strophanthidin without influencing performance." Unfortunately they failed to add the phrase "induced by toxic doses of acetyl strophanthidin." In Miller and Gilmore experiments the inotropic and potassium-losing effect of 50 µg of acetyl strophanthidin were determined on an isolated, donor supported dog heart preparation before and after DPH treatment (7.5 mg per kilogram). In our study the effects of continuous infusion of acetyl strophanthidin or ouabain (total dose, 1 to 2,000 µg) were determined before and after DPH (5 mg per kilogram) in the intact dog heart. The end point in the studies of Miller and Gilmore was steady state increase in ventricular force development. In our experiments the end point was digitalis toxicity manifested by ventricular tachycardia. No mention of an arrhythmia being encountered in the former experiments was made nor could it be expected with such low dose of acetyl strophanthidin. On the basis of their data, Miller and Gilmore conclude that "the antiarrhythmic efficacy of diphenylhydantoin in the presence of acetyl strophanthidin may not be related to its effect on total myocardial potassium balance." It seems inappropriate to describe the antiarrhythmic efficacy of DPH in the presence of acetyl strophanthidin when an arrhythmia is absent. Our previous data show that DPH alone has no effect on A-V potassium difference and in the presence of low doses of acetyl strophanthidin or ouabain does not significantly change the rate or total efflux of potassium from the heart.

Miller and Gilmore statement that "the cause of the *discrepancy* between the present results and those of Scherlag and associates is not apparent but may reflect the differences in the preparations used and in the experimental design" is a marked understatement. There are no discrepancies in those aspects of the two studies that are comparable; those aspects which are purported to be in disagreement are not comparable.

Benjamin J. Scherlag, Ph.D.
Cardiovascular Physiologist
Division of Cardiology
Mount Sinai Hospital
Miami Beach, Fla. 33140
Richard H. Helfant, M.D.
Chief, Division of Cardiology
Assistant Professor of Medicine
Presbyterian-University of
Pennsylvania Medical Center
Philadelphia, Pa. 19104

REFERENCES

1. Scherlag, B. J., Helfant, R. H., Ricciutti, M. A., and Damato, A. N.: Dissociation of the effects of digitalis on myocardial potassium flux and contractility, Amer. J. Physiol. 215:1288, 1968.
2. Helfant, R. H., Ricciutti, M. A., Scherlag, B. J., and Damato, A. N.: Effect of diphenylhydantoin sodium (Dilantin) on A-V potassium difference, Amer. J. Physiol. 215:880, 1968.

Reply

To the Editor:

I would like to thank Dr. Scherlag for sending me a copy of his letter to you of Sept. 9. I offer this reply in the hope that the AMERICAN HEART JOURNAL will be willing to serve as a forum for comment on the relation between the actions of diphenylhydantoin (DPH) and the cardiac glycosides. I would also like to thank Dr. Scherlag for his initiative in promoting a direct exchange of views between the laboratories.

My understanding of the sequence of events in the experiments of Helfant and associates[1] is the following. Administration of acetyl strophanthidin (ACS) or ouabain induces a primary loss of myocardial potassium. This primary loss of potassium induces ventricular tachycardia which, in turn, causes a secondary loss of myocardial potassium. Indeed, according to Fig. 1 of either Scherlag and colleagues or Helfant and his group, most of the coronary arteriovenous potassium *concentration* difference observed during digitalis toxicity and tabulated in Table I of Scherlag and co-workers would appear to be accounted for by this secondary loss of potassium. The potassium analysis system used by Dr. Scherlag and his associates

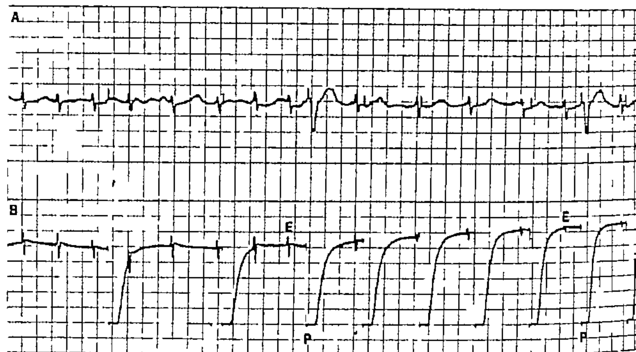


Fig 3 Simultaneous endocardial and surface ECG A Surface ECG showing inappropriate pacemaker firing with occasional capture. B The endocardial lead discloses a clue to the mechanism for malfunction by demonstrating variation in the amplitude of QRS complexes. (E): Complexes 3 6 and 8 to 14 are smaller in amplitude and fall below sensing threshold and unlike complexes 2, 5 and 7 are unable to inhibit subsequent discharge of the pacemaker (P)

spikes being of high voltage drive the transmitter into saturation and thereby tend to mask subsequent QRS response. A simultaneously recorded surface lead (Fig 1 B) illustrates the lack of ventricular capture, except for complexes 6 and 8

2 PVC's, which on the surface lead are larger than the patient normally conducted QRS may be so small on the endocardial lead as to fall below the 1 to 2 mv sensing threshold (Fig 2) The low amplitude of endocardial PVC may explain the recent report by Samet and associates of pacemaker failure to detect a PVC

3 A recording from the bipolar catheter can be useful in evaluation of the contact between endocardium and catheter Unsatisfactory contact is suggested by variation of 25 per cent or more in the amplitude of successive QRS complexes or by sudden shifts in baseline (Fig 3) The former has been described for floating pacemaker catheters and has been associated with a high failure rate.

We conclude that there was no significant difference in the performance of the three types of pacemakers. Recording from the bipolar catheter is of value in assessing whether the catheter is in good electrical contact with the endocardium. This information is not necessarily provided by x ray or the surface ECG. A battery-operated unit for endocardial recording provides a margin of safety against low current electrical shock.[4] On the other hand line-operated equipment may be hazardous unless meticulous grounding and isolation are practiced.

We believe that this approach will not only facilitate early detection of pacemaker malfunction but also will help to resolve some of the other baffling problems associated with temporary pacing.

Irene Hsu M.D
Associate Professor of Medicine
Fredric A Siegel M D B S.E E
Associate in Medicine
George Maskew, M.D
Fellow in Cardiology
George Washington University Medical Center
Department of Medicine
Washington, D C
Dwight D Barth
Chief Engineer
Bond Research Laboratory
Boston Mass.

REFERENCES

1 Samet, P Center S Linhart, J W and Keller W Selected current aspects of cardiac pacing Amer J Cardiol 23 702 1969
2 Castellanos, A. Jr and Lemberg L. Electrophysiology of pacing and cardioversion, New York, 1969 Appleton Century Crofts, p. 20.
3 Bruner J M R Hazard of electrical apparatus, Anesthesiology 28:396, 1967
4 Staewen W S Lubin D M weer M M and T batanik B The significance of leakage current in hospital electrical devices, Sinai Hosp. J 15:3 1969

loss. Dr Scherlag states in his letter that he has previous data[1] that DPH in the presence of ACS or ouabain does not change the rate or total efflux of potassium from the heart. These findings could be in agreement with those of Miller and Gilmore. At the risk of appearing to lack politeness, I find that I cannot concur with the statement in Dr Scherlag letter for two reasons. First, I find no data available in the article by Helfant and colleagues[2] on the effect of DPH on the loss of myocardial potassium induced by low doses of ACS or ouabain. Second, Dr Scherlag system does not measure the total efflux of potassium from the heart because he does not measure coronary blood flow

The differences in experimental design alluded to by Gerlings and associates[3] were purposely understated because we felt that they were obvious to workers in the field. To be more explicit, Table I has been composed.

In closing, I would again like to thank Dr Scherlag for the opportunity to discuss the interpretation of data collected from both laboratories on this problem. I would welcome and appreciate any further comments from Dr Scherlag. In addition, if Dr Scherlag is amenable, publication of this exchange in the AMERICAN HEART JOURNAL would, I believe, be of interest to those in the cardiovascular field.

David T Miller
Department of Physiology
College of Medicine
The University of Nebraska
Omaha, Neb 68105

REFERENCES

1 Scherlag, B J Helfant, R. H Ricciutti, M A., and Damato, A. N Dissociation of the effects of digitalis on myocardial potassium flux and contractility Amer J Physiol. 215 1288, 1968.
2. Helfant, R. H Ricciutti, M A., Scherlag, B J and Damato, A. N Effect of diphenylhydantoin sodium (Dilantin) on A-V potassium differences, Amer J Physiol. 215:880, 1968
3 Gerlings, E D Miller D T and Gilmore, J P Oxygen availability determinant of myocardial potassium balance, Amer J Physiol 216:559 1969
4 Miller D T and Gilmore, J P Influence of diphenylhydantoin on the inotropic and potassium losing effects of acetyl strophanthidin, AMER HEART J 80:223 1970

Pathogenesis of "rheumatic" heart disease

To the Editor

The hypothesis of Burch, Giles, and Colcolough (Pathogenesis of "rheumatic" heart disease, AMERICAN HEART JOURNAL, October 1970), relegating to the virus an etiologic role in the pathogenesis of rheumatic heart disease, is plausible and thought provoking. The challenge it will pose to the established concepts will certainly stimulate critical reappraisal of the role of streptococcus in the etiology of rheumatic heart disease.

In my opinion, the virus theory seems to have particular merit when applied to rheumatic chorea. Neurotropism is recognized characteristic of viruses and, moreover the extrapyramidal system is favored site of localization (e.g., the influenza pandemic and the associated encephalitis of 1919 that led to the postencephalitic Parkinsonism) The lack of evidence of streptococcal infection, the absence of acute phase reactants, and the prolonged course of the illness all seem to fit in the viral theory

Investigations for possible viral infection in patients with acute rheumatic fever carditis, and particularly in those with chorea, may throw further light on the problem.

Vachen V Kalbian, M.D
Physician in Charge
Rheumatic Fever Clinic
Childrens' Medical & Surgical Center
Johns H pkins Hospital
Baltimore, Md.

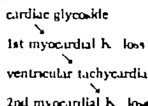
Recording of A-V nodal activity

To the Editor

One of the major conclusions in the paper by Damato and associates (Recording of A-V nodal activity in the intact dog heart, AMERICAN HEART JOURNAL, September 1970) is that A-V nodal rhythms arise in the His bundle or coronary sinus area and not the A-V node. This conclusion is entirely based on the absence of the N potential in A-V nodal rhythms. It is difficult to discern whether many of these recordings of "N" potentials are part of atrial depolarization or represent all or part of A V nodal activation. However it appears to us that the pitfalls in the interpretation of several of these nodal humps and their behavior under various conditions have not been avoided by the authors. Fig. 7 shows the progressive widening of the N potential as function of vagosympathetic trunk stimulation and atrial pacing. Another reasonable interpretation is that as the A-H time widens more of the superimposed ventricular T wave (as seen on the intracardiac lead) is exposed. This is apparent if one notes that the P wave of the surface ECG moves through the preceding ventricular T wave and if one also observes the shape and relative position of the slow T wave potential as clearly seen on the second trace (intracardiac lead, HBE) of Fig. 6.

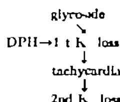
In addition, the authors claim that the nodal hump extends from the A wave to His bundle deflection and with slowed A V conduction this wave decreases in amplitude and duration. In many cases distinct isoelectric segment is seen preceding the His bundle deflection. If this isoelectric segment represents some part of the A-V nodal potential, then the His bundle rhythm (A-V nodal rhythm) could be arising in the A V node since an isoelectric period precedes the His bundle deflection in all their

does not exhibit sufficient time resolution to permit one to state whether the tachycardia preceded the change in A V potassium *concentration* difference or vice versa However in view of the well known transient loss of myocardial potassium with increases in heart rate it would be invoking undue complexity to say that this potassium loss was not secondary to the tachycardia To summarize the points upon which I think Dr Scherlag and I agree the following diagram is offered



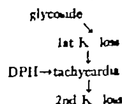
The arrows indicate causal relations.

Dr Scherlag and I differ I believe as to how one should positio the action of DPH in stopping this chain of events. If I understand Dr Scherlag interpretation correctly he would place the effect of DPH on the primary potassium loss. That is, DPH reverses the primary potassium loss and causes a gain



It not immediately clear however how an agent DPH which, as Helfant and colleagues have shown does not tself cause an uptake of myocardial potassium could ca se such an uptake n reversing the effect of an agent— digitalis—which only causes a loss This, really is the crux of the question The matter becomes clearer with an additional piece of information Gerlings and co-workers using a system which *continuously* measures the *amount* of myocardial potassium loss or gain, have consistently observed that upon ret rn to a lower heart rate after a period of artificially ind ced tachycardia, the heart *gains* potassium. In fact, the heart always regains almost exactly the *amount* that t lost. This point is illustrated in Fig 1 In all experiments of this type, coronary arterial K⁺ levels were consistently only a few hundredths of a milliequivalent above or below the steady state venous level. If coronary flow is low the period in which coronary venous potassium concentration is lower than coronary arterial potassium concentration may indeed be prolonged.

The point is that DPH could appear to be directly involved in an uptake of potassium by the myocardium simply by removing the tachycardia. This explanation and the evidence from Miller and Gilmore[4] suggest that the site of action of DPH in the diagram is not upon the primary potassium loss but rather upon tachycardia, for example



Actually I think Dr Scherlag and I probably agree that DPH has no effect on the primary potassium

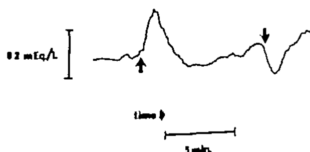


Fig *1* The K concentration of blood from the coronary sinus of an in vi o dog heart is shown as a function of time. At the first arrow heart rate was increased from 90 to 180 beats per minute by means of electrical st muli delivered through wire electrodes sewed to the right trium. Heart rate was returned to 90 beats per minute at the second arrow Arterial potassium concentration was constant throughout the maneu er

Table I Differences in experimental design

Exp parameter	*Helfant and associates*[1]	*Miller and Gilmore*[4]
Heart rate	Uncontrolled	Controlled
Coronary blood flow	Unkn wn and uncontrolled	Known and controlled
Level of cardiac neural input	Present b t unknown and uncontrolled	Not present
Circulating catechols	Probably variable	Probably not variable
Coronary A V Pot diff	Unknown	Known
Coronary K⁺ measurement	Intermittent	Continuous
Drug level seen by whole animal	As high as heart	Much lower than heart

Demand pacing in carotid sinus syncope

To the Editor

The paper by Drs. Voss and Magnin entitled "Demand pacing in carotid sinus syncope," in the April, 1970, issue of the AMERICAN HEART JOURNAL, states that hypersensitivity of the carotid sinus was the cause of episodic asystole and unconsciousness in an 81 year-old woman, subsequently treated successfully by transvenous demand pacing. An alternative explanation of the pathophysiology involved when carotid sinus massage causes asystole should be mentioned. I have been repeatedly impressed that patients who are experiencing intermittent syncope and who have electrocardiographic evidence of incomplete bilateral bundle branch block (right bundle branch block and left anterior hemiblock) respond to any vagal-stimulating maneuver with complete heart block and momentary asystole. Indeed, carotid massage has proved a useful means of demonstrating conclusively that intermittent complete heart block has been the cause of the patient's symptoms. I have presumed that the "hypersensitive" organ in the reflex arc in these situations is the diseased cardiac conducting system and not the carotid sinus.

It would be pertinent to know if the electrocardiogram in the patient reported showed any evidence of bundle branch block and if the effect on heart rate of any other vagal-stimulating maneuver was noted.

Richard E. Fearon, M.D., F.A.C.C.
Attending in Medicine
Yale-New Haven Hospital
New Haven, Conn.

Reply

To the Editor

We would like to thank Dr. Fearon for his comment in regard to our paper "Demand pacing in carotid sinus syncope." Our patient did not have bundle branch block. Electrocardiograms before and after the pacemaker implantation never demonstrated a complete heart block. Repeated carotid stimulation consistently produced prolonged asystole which was corrected by the pacemaker. Other vagal-stimulating maneuvers were not used. The patient has remained asymptomatic since the pacemaker placement two years ago. We do not believe that the pathophysiological mechanism described by Dr. Fearon was responsible for our patient's symptoms.

Dieter M. Voss, M.D.
George E. Magnin, M.D.
Department of Internal Medicine
Marshfield Clinic
Marshfield, Wis.

records. Watanabe and Dreifus[1] have shown that when the A V node is the pacemaker intranodal conduction is markedly slowed explaining the high incidence of exit block in A V nodal rhythms. It seems apparent that the amplifier filter settings of 40 to 200 Hz are particularly inappropriate to resolve this question Indeed Scher and colleagues[2] showed slow potentials preceding His bundle deflections in A V nodal rhythms

Furthermore the authors state that potentials recorded from other areas of the atria did not show similar slow waves following the initial rapid deflection of atrial activation. If the gain of the other recordings were identical to the recordings from the A V node and His bundle region, I believe that the slow wave after the atrial potential from the Bachmann's bundle area (Fig. 14) would be comparable to the N deflection seen in several of the other illustrations.

What is particularly puzzling is the apparent similarity of the simultaneous recordings of the N H and RB potentials made with the close bipolar wires and the electrode catheter (Fig 3) The wires inserted through a single needle would be approximately 1 to 2 mm apart at the most whereas the electrodes on the catheter are 10 mm. apart. It is difficult to understand how both of these electrodes could record electrical events arising from tissues that are separated spatially by at least 12 to 15 mm

Benjamin J Scherlag Ph D
Cardiovascular Physiologist
Mount Sinai Hospital of Greater Miami
Miami Beach Fla

REFERENCES

1. Watanabe, Y and Dreifus, L. S Sites of impulse formation within the atrioventricular junction of the rabbit, Circulation Res. 22:717 1968.
2. Scher A M Liikane J Rodriguez M I and Young, A C Slow potential change in the atrioventricular node Science 121:873 1958.

Reply

To the Editor

Dr Scherlag has raised several questions in his letter Some of these questions are related to the technique used to record electrical activity of the specialized conducting tissues and others are addressed to the interpretation of our findings.

Our conclusions that so-called A V nodal rhythm arise from the regions of the bundle of His or coronary sinus is not, as Dr Scherlag states, based *entirely* on our presented findings. Our findings support the views of others and it is on the total available evidence that we have come to our conclusion. In our judgment the available scientific evidence for the traditional concept of upper middle, and lower A V nodal rhythms is less convincing than the evidence (both direct and indirect) supporting bundle of His and coronary sinus rhythms. Furthermore, the electrocardiographic pattern of so-called upper middle, and lower A V nodal rhythms can be reproduced by stimulating the bundle of His or coronary sinus. Pervenous pacing studies of the A-V node in man are far from convincing and alternative explanations can be applied to explain the results.

The interpretation of the N potential must of course be made in context. Having established and recognized the morphological characteristics of the N potential during sinus rhythm (where it is not obscured by a ventricular T wave) the progressive changes which occur during certain interventions can be followed with reasonable certainty At times, a large ventricular T wave can distort the N potential when interventions cause them to be superimposed. Dr Scherlag has chosen to ignore the nonisoelectric N potential which is associated with QRS complexes which precede (not illustrated) and follow the junctional beat as illustrated in Fig. 9 I would expect that if a so-called upper or middle nodal rhythm arose in the upper or middle portion of the A V node a major part of the notched N potential would precede the H deflection. It is conceivable that a pacemaker located in the N H region would not be associated with significant notched wave preceding the His deflection Under these circumstances one might expect to see the retrograde N potential distort the segment between the His deflection and the onset of ventricular activation.

Dr Scherlag states that the slow wave following the BB electrogram of Fig 14 would be comparable to the N potential if the gain was increased. I would like to call to Dr Scherlag's attention the fact that in Fig 8 the N potential precedes the BB and all other recorded electrograms. While it is true that slow waves, which may or may not resemble the N potential (usually they do not) can be recorded from other sites within the heart such recordings do not of themselves validate our N potential recordings. What is important in this regard is that these waves be interpreted within the context. The N potential as we have recorded it has certain characteristics which are consistently obtained within a specific region of the heart. Along these same lines, a slow fast deflection can be recorded in areas of the atria The fast deflection can resemble the His deflection Such a recording does not invalidate the true His potential. Obviously both deflections have similar response characteristics. The same may be true for the A V node and other slow waves.

It is apparent that the plunge wires which may be spaced 1 to 2 mm apart do in fact record electrical activity which is outside the 2 mm field This is evidenced by the fact that plunge wires may record atrial or ventricular activity which encompasses the total P or QRS complexes of the surface ECG The specificity of any deflection of course depends in large measure upon the proximity of the electrodes to a specific anatomic region Furthermore the A V node and bundle of His are not straight line structures. Certainly electrodes spaced 10 mm apart on a curved catheter can include the electrical field of the A V node and bundle of His.

Anthony N Damato, M.D
Cardiopulmonary Laboratory
United States Public Health Service Hospital
Staten Island N Y

American Heart Journal

May 1971 Volume 81 Number 5

Editorial

The artificial cardiac pacemaker

Hilbert J. Th. Thalen, M.D.
Groningen, The Netherlands

At the end of the eighteenth century Vassali, Giulio and Rossi reported to the Italian Society of Sciences their results with stimulation of various organs and muscles of decapitated criminals. They stated that "le coeur qui dans l'individu soumis au galvanisme jouissait encore d'une grande vitalité, présenta aussitôt des contractions très visibles et assez fortes."

This was one of the first successful attempts to stimulate a human heart post mortem. It was 1932, however, before Hyman[1] succeeded in constructing an apparatus of which he said three years later: "since it was conceived as a substitute for a nonfunctioning normal sinus nodal pacemaker, it has been called the artificial pacemaker." This first artificial pacemaker, which weighed 7.2 Kg., received its energy from a spring motor regulated by a ballistic governor with a ratchet handle for rewinding of the motor every 6 minutes. This apparatus did not gain full acceptance; further development of the artificial pacemaker came twenty years later when Zoll in 1952, reported the successful use in two patients of an artificial external electrical pacemaker for arousing the heart from ventricular standstill.

A disadvantage of this unit was the fact that it used skin electrodes. Better results were obtained with electrodes placed directly on the ventricular wall, initiated by Weirich and colleagues in 1957, or with catheter electrodes inserted via the veins into the right ventricle, a technique developed by (among others) Furman and Robinson after experiments of Bigelow and associates.[4] Due to the fact that some components of the electronic circuit were large and had a low efficiency (the vacuum tubes required a high voltage and relatively large heater current), the stimulating apparatus proper had to be placed outside the body. To avoid skin perforation by the electrode Abrams and associates[7] used the principle of magnetic impulse transmission by way of an external primary coil placed in alignment with a subcutaneous secondary coil connected to the electrode. A modification of this principle, electromagnetic impulse transmission by way of radiowaves, has been developed by Glenn and associates[8] and Cammilli and associates.[9] Development of transistors made the vacuum tubes obsolete. Transistors work at low voltages available from batteries and require no heater current; their dimensions and the use of batteries made possible the construction of implantable units. In 1959 Elmqvist and Senning[10] reported the first implantable pacemaker. It used nickel cadmium batteries that had to be recharged inductively from time to time because of

From the Clinic of Internal Medicine (Dir. Prof. Dr. H. Mandema), Department of Cardiology (Dir. Prof. Dr. J. Nieveen), University Hospital, Groningen, The Netherlands.

Vol. 81, No. 5, pp. 583-590, May 1971

Book reviews

Lehrbuch der Auskultation und Perkussion Inspektion und Palpation. By Klaus Holldack. Stuttgart 1970 Georg Thieme Verlag, 170 pages.

In spite of the recent progress in medical instrumentation the time-honored methods of inspection, auscultation, percussion and palpation are still important according to the author. The experience is not uncommon that small accumulations of fluid in the thorax may escape detection by x-ray and may be diagnosed or at least suspected by percussion. There is however a tendency toward increasing reliance on instrumental diagnosis, so that the art of percussion as practiced by experienced internists of 40 years ago has been lost to a certain degree, as stated in Dr Oehme's foreword. With the limitation of the scope of any general textbook on physical diagnosis, perhaps not enough space can be devoted to these older diagnostic methods which require only a stethoscope. In contrast, the new diagnostic methods have become so expensive that even in wealthy countries they cannot be paid (Introduction, p. 1).

There is actually a large amount of information which can be obtained from the simple methods as documented in the volume which is particularly valuable for physicians in rural communities.

The book starts with examination of the head and proceeds to examination of the neck, thorax, abdomen, and peripheral circulation. Examination of the thorax takes the largest space (pp. 32 to 121) as may be expected. Auscultation of the thorax is illustrated by phonocardiograms, with occasional electrocardiograms and carotid pulse tracings. In addition, there are two phonographic records. First record—A, percussion B, Nebengeräusche (including pleuritic rub); second record—C, mitral valvular disease, and D aortic valvular disease. The book is lavishly illustrated. This is the seventh edition (the first appeared in 1955) which shows the favorable acceptance in Germany. The text is quite comprehensive and well presented. It fills what has become a gap with the progress of electronic diagnostic methods.

Ultraschallkardiographie. By Willibald Schmitt and Heribert Braun, unter Mitarbeit von H. Kreuz. Stuttgart 1970, Georg Thieme Verlag

This is a brief but succinct description of the technique and application of echocardiography to clinical research and clinical cardiology. The authors describe their method clearly with adequate illustrations. These descriptions include discussions of the theory of sound and echocardiography as well as the equipment used. The applications to clinical states are nicely presented and profusely and well supported by echocardiograms recorded simultaneously with electrocardiograms and phonocardiograms. The common applications are included with many case reports. This is a good book on a subject that has definite applications to clinical and research cardiology.

found in the R wave-controlled or demand pacemakers.

The R wave-controlled pacemaker has been constructed in two versions triggered and blocked. The R wave-triggered pace maker reported by Donato and Denoth[22] in 1966, is a modification of the P wave-triggered pacemaker It detects ventricular activity and stimulates the ventricles after a very short delay time of some milli seconds. If there is sinus rhythm, the stimu lating impulse will occur in the ventricular depolarization if there is asystole, the unit will stimulate the heart after a preset time. The R wave-blocked pacemaker already reported in an external version by Leatham and co-workers[23] in 1957 and by Sykosch and co-workers[24] in 1963 also stimulates the heart after a preset asystole however in case of ventricular activity the R wave does not trigger the output circuit of the pacemaker but blocks the output circu t, no stimulation impulse being given to the heart. This results in less energy consumption in regard to the triggered unit as the stimulating impulse is saved. Recent re ports describe a combination of an atrial triggered ventricular blocked unit, the atrial synchronized demand pacemaker[25] and also a bifocal atrioventricular demand stimulator[26] Both stimulators are rather complicated and consume much energy

The choice of the pacemaker to be im planted is complicated especially when a first implantation is concerned According to the point of view of our group P wave-triggered pacemakers should be implanted in the young patients (of whom there are few) For the other patients a choice has to be made between the fixed rate and the demand pacemaker The latter in the R wave-blocked type consumes less energy when it is blocked than the former but more, because of its detection circuit, when it is stimulating the heart continuously whereas the R wave-triggered pacemaker consumes the most energy of the three types.

A follow-up study of 141 patients stimulated with fixed-rate pacemakers during three years revealed that the sinus rhythm returned in 40 patients. This occurred in 21 patients in the first half year after implantation, in 8 patients in the second half year and in 10 patients in the second year for a total of 39 patients (or 97.5 per cent) in the first two years. There was only one patient in the third year[26] This means that within the implantation time of the first pacemaker the choice of the second pacemaker easily can be made as, for the reasons mentioned a fixed-rate pacemaker is more efficient in those cases wherein no proper heart rhythm has returned The other patients in our clinic get an R wave-blocked pacemaker

The choice of the first pacemaker is not so easily made. A safe method would be to implant at first an R wave-blocked pacemaker in all patients. In case of long persisting A V block, however we implant a fixed-rate unit and counteract the eventually proper heart activity with beta blocking agents. The fact, however that we have to use these drugs in some cases means that our choice is not always the right one.[27]

At the World Congress on long term cardiac pacing where a survey of the pace maker activity in various countries in 1969 was given, it developed that in America and Canada about 80 to 85 per cent of the units were of the noncompetitive type. In Europe this percentage was a little lower and ranged between 40 and 60 per cent (England, 40 per cent Italy 56 per cent Scandinavia, 35 to 57 per cent Holland, 38 per cent and Belgium, 49 per cent)[28] In France recently a lesser acceptance of noncompetitive units and an increased application of fixed-rate units because of the longer lifetime of the latter was noted.[29]

Besides the pacemaker proper an important part of the stimulation unit is formed by the electrode or that part of the electrode circuit where the electrical impulse reaches the heart muscle. This can take place at the endocardium with transvenous electrodes or at the epicardium or myocardium with the transthoracic approach by way of thoracotomy and retrosternal or transdiaphragmatic incision. At one time these latter electrodes were preferred, but at present the transvenous approach is used in about 85 to 90 per cent.[28] This might be explained by the fact that the transvenous approach is less complicated and that the danger of dis-

their small capacity of 60 mAh With the use of nonrechargeable mercury cells with a capacity of 1 000 mAh implantable pacemakers that could function for years were constructed shortly later by many workers.[11,13]

The electronic circuit of an implantable pacemaker can be divided into two sections the impulse forming circuit and the output circuit The impulse-forming circuit determines the duration and the frequency of the impulses. Two different circuits are used (1) the blocking oscillator circuit which includes a transformer and determines the time interval by self induction and an RC circuit and (2) the free running multivibrator circuit which includes no transformer and determines the time interval by RC circuit only Both circuits open for a certain length of time (impulse duration) and with a certain frequency (impulse frequency) a transistor of the output circuit resulting in a current (impulse current) in the output circuit in which the stimulation electrodes are incorporated

The output circuit determines the shape and amplitude of the impulse and there are three types. In the first type of circuit the condenser in the output circuit charged during the impulse interval to a certain voltage is discharged according to Ohm s law ($I = i \times Re$) where the impulse current (i) is determined by the condenser and the resistance in the electrode circuit (Re) Changes in this resistance will influence the current but not the voltage which gives this circuit its name of voltage circuit In the second type of circuit a large internal resistance (Ri) is placed in series with the electrodes Ohm s law being here $V = i \times (Ri + Re)$ As the internal resistance (Ri) is far higher than the resistance of the electrode circuit (Re) changes in Re will be small in relation to Ri and the impulse current not being influenced by changes in Re will therefore be constant giving this circuit the name of current circuit. As a large Ri necessitates a large voltage to keep a sufficient current (i) most current circuits require such an Ri that the current is almost constant The third output circuit being applied in pacemakers is the current limited voltage circuit. This is a voltage circuit but the maximal current in the circuit is limited, preventing a (too) large current impulse to circulate when there is a low resistance in the electrode circuit [14]

The fixed rate pacemakers can be classified in various types according to their circuits. There is the blocking oscillator type with current circuit[11] or with voltage circuit [19] and the free running multivibrator type with current circuit[13] or with current limited voltage circuit.[14,17]

These pacemakers all have a fixed frequency although by transcutaneous needles[11] or by magnetic switch[14] variations can be made in frequency and impulse amplitude.

In fixed rate stimulation atrioventricular coordination is not maintained which results in the loss of the greater part of the contribution of the atrium to the cardiac output Although this loss can be compensated for by reserve mechanisms (e.g increased stroke volume in submaximal stress) during stress losses in cardiac output of 5 to 15 per cent of the optimal values may result.[18] Attempts to restore A V conduction by an electronic A V bridge resulted in 1963 in the P wave–triggered pacemaker [17] which detects the atrial depolarization and starts after a delay time (PQ time) the pulse forming circuit. The atrial depolarization is detected by way of either an epicardial or an endocardial atrial electrode. Detection of the atrial depolarization from the ventricles has been unsuccessful [19] The P wave–triggered pacemaker however consumes energy because of the amplification of the small P wave signals and the delay circuit and in about 20 per cent of the cases the atrial activity is unsuitable as trigger [18]

In addition to improved hemodynamic conditions, this pacemaker has the advantage that in case of return of sinus rhythm it overcomes the danger of interference resulting in ventricular tachycardia and fibrillation caused by the stimulating impulse occurring in the vulnerable period Although this event is not so common and depends among other things, on the fibrillation threshold of the myocardium [20] return of sinus rhythm has been seen rather frequently in cardiac pacing (20 to 40 per cent) A less energy-consuming solution was

With increasing impulse duration the threshold current decreases until it reaches a minimal level—the rheobase Further increase in impulse duration thereafter does not result in decrease of the stimulation threshold The relation between impulse current and impulse duration results in the chronaxie rheobase curve, where the chronaxie equals the minimal impulse duration required to cause a heart contraction, at an impulse current of twice the rheobase These chronaxie rheobase curves are identical for myocardial and endocardial stimulation. The same holds for the voltage threshold, whereas the curve of energy threshold vs. impulse duration is loop shaped with a minimum at the impulse duration corresponding to the chronaxie. The charge threshold increases with increasing impulse duration[24] Initially the impulse duration of implantable pacemakers was established at 1.8 to 2 0 msec. Measurements showed that this impulse duration resulted with most pacemakers in a relative threshold of 20 to 40 per cent of the total pacemaker output and a safety margin of 60 to 80 per cent Long term follow-up did not demonstrate a further threshold increase after the initial postoperative period.[14] Monitoring of the stimulation threshold and proper heart activity with implanted pacemakers has become possible by the development of the threshold pacemaker[27,28] With this pacemaker the battery voltage can be reduced externally by way of induction Because of the stable relatively low threshold the impulse duration has been decreased in the past year to 1 0 to 1.5 and even 0 8 msec. as a smaller impulse duration yields less current drain and longer pacemaker life-time. A narrow impulse has, however a smaller safety margin and may increase the danger of exit block due to threshold changes.

Impulse frequency variations between 50 and 110 impulses per minute have almost no influence on the stimulation threshold.

The last factor influencing the threshold is the electrode circuit proper Implantation of intramural electrodes at various sites of the heart did not result in significant threshold variations. At endocardial electrodes, with the electrode tip between the trabecular muscles, the same is recorded. Threshold variations are met with a poor contact between electrode and heart muscle and with electrode displacements as can be seen with endocardial electrodes, where dislocation into the outflow tract or into the right atrium may cause such a threshold rise that exit block results.

Besides the site of the stimulation electrode the site of the indifferent electrode has also been investigated. We have not been able to record differences in the current threshold with the indifferent electrode located in the myocardium (bipolar stimulation) or elsewhere in the body (monopolar stimulation) as long as the negative electrode had a lower cathodal threshold than the anodal threshold of the indifferent electrode. When in bipolar stimulation the cathodal threshold increases beyond the anodal threshold of the indifferent electrode then the stimulation threshold is determined by the indifferent electrode and not by the negative electrode.

Normally the stimulation threshold is determined by the negative electrode. Variations in the electrode dimensions are related to changes in the stimulation threshold a greater electrode surface entailing a higher stimulation threshold. (The threshold increase is relatively greater for the current threshold than the voltage threshold because a greater electrode surface yields a lower ohmic resistance, as will be explained later) This is explained by the fact that for activation of the heart muscle a minimal current density is needed. With an electrode with a greater surface, the area where the minimal current density is needed increases, resulting in a rise of stimulation threshold It can also be stated that the stimulation threshold is related to the current density in the intact cardiac tissue at the electrode. This explains the threshold rise recorded after the initial electrode implantation. After implantation fibrous tissue originates around the electrode, causing a greater distance between electrode and active myocardial tissue and an increase in stimulation threshold. The threshold rise stabilizes after 4 to 6 weeks and is not related to an increase of the resistance in the electrode circuit. In fact, this resistance decreases during the first

location of the transvenous electrode has lessened because of improved electrode design (e.g. the barbed tip). Recently the cephalic vein has been used rather than the jugular vein for catheter introduction because this produces fewer dislocations due to body and arm movements and pressure necrosis which can occur near the introduction site of the jugular vein in the neck is not seen at this location. Another advantage of the transvenous electrode is the fact that in case of infections near the pacemaker pocket, pacemaker and electrode can be replaced much more easily in regard to transthoracic electrodes. The endocardial atrial electrode, however, still poses dislocation problems that have not been solved so far. With the P wave triggered pacemaker mostly epicardial atrial electrodes are used—implanted via thoracotomy or mediastinoscope.[30]

The stimulation electrode entails one of the most important parameters in cardiac stimulation—the stimulation threshold, which may be defined as the minimal stimulus required to cause a specific heart reaction, i.e., contraction of the heart muscle. The stimulation threshold can be measured in milliamperes as current threshold, in voltage as voltage threshold, in microjoules as energy threshold, or in microcoulombs as charge threshold. Mostly two or more of these thresholds are recorded whereas the other thresholds can be calculated. Thus the charge threshold equals the current threshold multiplied by the impulse duration, the voltage threshold equals the current threshold multiplied by the resistance in the electrode circuit, the energy threshold equals the square of the current threshold times the resistance in the electrode circuit. This means that a threefold rise of the current threshold entails a ninefold rise of the energy threshold whereas the voltage and energy thresholds are related not only to the current but also to the complicated resistance of an electrode circuit.

The stimulation threshold is influenced by three different groups: variations of the myocardium, of the stimulation impulse, and of the electrode circuit proper.

Variations of the myocardium may be produced by electrolytes and drugs among other things. Sowton and Barr[31] and Preston and Judge[32] have reported an increase of the stimulation threshold with increasing potassium levels and reverse. In this regard the influence of insulin and glucose must be mentioned.

The influence of corticosteroids varies. Glucocorticosteroids (prednisone and methyl prednisone) decrease the stimulation threshold but mineralocorticosteroids (aldosterone) increase it.

Administration of sympathomimetics (epinephrine, norepinephrine, ephedrine, and isoproterenol) entails initially a threshold decrease. This may explain the threshold decrease met with exercise that can be reversed by administration of beta blocking agents (e.g., Inderal). These beta blocking agents do not influence the stimulation threshold during rest.

Antiarrhythmic drugs like chinidine, procainamide, lidocaine, and digitalis are reported to have no influence on the stimulation threshold because they should affect the action potential and not the rest potential of the myocardium cells. On the latter, however, there is no complete agreement so far.

Important in regard to pacemaker design is the influence of the stimulation impulse on the threshold.[14] Electrode polarity affects the stimulation threshold, negative stimulation yielding a lower threshold than positive stimulation. The lower negative threshold is explained by the fact that normal depolarization of the heart is initiated by cathodal stimulation, the heart cell having a rest potential of 85 to 95 mV and the extracellular side being positive with respect to the intracellular side. The anodal stimulation could be explained as "break" excitation at the end of the positive impulse,[33] although a "make" excitation at the anode also has been suggested.[34]

The impulse shape also influences the stimulation threshold. Variations in the shape of triangular impulses did not influence the threshold current or charge significantly but in relation to rectangular impulses the latter yielded the lower threshold current but the higher threshold charge.[14, 35]

The most important parameter of the impulse is, however, the impulse duration

implantation periods did not exceed the lifetime of battery-powered pacemakers because of deterioration of the discs supplying the energy

More promising seems application of nuclear energy The isotope plutonium-238 with a half-life of 86 4 years has been used for this purpose. The α-radiation is converted by thermocoupling into electrical energy After animal experiments, the first atomic-powered unit was implanted clinically in April 1970 in a patient in France.[48] It contains 150 mg of plutonium 238 isolated by tantalum and produces a voltage of 0.5 v transformed to a 6 v pacemaker impulse. Almost the same unit has been developed in England and so far five have been implanted clinically [49] Radiation at the pacemaker surface is about 3 to 4 millirem per hour whereas the batteries themselves can stand temperatures up to 850° C and pressures of 800 Kg per square centimeter In America, also nuclear powered pacemakers are under construction, but another thermocoupling has been used and posed some problems that have made clinical application not acceptable so far

The nuclear-powered pacemakers have a calculated lifetime of 10 years when we consider their power source, but component reliability also influenced by radiation, might become a limiting factor of these units. It can be expected that in the near future more implantations will be performed and both European groups plan an extensive use of their batteries within 1 to 2 years for cardiac pacemakers.[33]

This transformation from the 7.2 Kg spring-motored stimulator to the nuclear powered implantable unit clearly illustrates the progress that has been made in the field of cardiac stimulation. At present the artificial cardiac pacemaker in combination with the pacemaker follow-up clinics and their pacemaker analysis systems, is a generally accepted electrotherapeutic that is being applied in an increasing number of patients.

We gratefully acknowledge the cooperation of Prof. Dr Jw van den Berg (Lab. for Medical Physics, State University Groningen) Prof. Dr J N Homan van der Heide (Dept. of Thoracic Surgery), Prof Dr J Nieveen (Dept. of Cardiology) and the colleagues at the Groningen University Hospital.

REFERENCES

1. Aldini, J Essai théorique et expérimental pour le galvanisme avec planchkes, Paris, 1804, L'Imprimérie de Fournier fils.
2. Hyman, A. S.: Resuscitation of the stopped heart by intracardial therapy Clinical point of view U S. Naval Med. Bull. 33:205, 1935.
3. Zoll, P N Resuscitation of the heart in ventricular standstill by external electrical stimulation, New Eng. J Med. 247 768, 1952.
4. Weirich, W L., Gott, V L., and Lillehei, C. W The treatment of complete heart block by the combined use of a myocardial electrode and an artificial pacemaker Surg. Forum 8:360, 1957
5. Furman, S., and Robinson, G. Stimulation of the ventricular endocardial surface in control of complete heart block, Amer Surg. 150:841 1959
6. Bigelow W G., Callaghan, J C., and Hopps, J A.: General hypothermia for experimental intracardiac surgery Amer. Surg. 132:531 1950.
7. Abrams, L. D Hudson, W A., and Lightwood, R.. A surgical approach to the management of heart block using an inductiv coupled artificial cardiac pacemaker Lancet 1 1372, 1960.
8. Glenn, W W L., Mauro, A., Longo, E., Lavietes, P H., and Mackay F J Remote stimulation of the heart by radiofrequency transmission, New Eng. J Med. 261:948, 1959
9. Cammilli, L., Pozzi, R., and Drago, G.: Remote heart stimulation by radiofrequency for permanent rhythm control in the Morgagni-Adams-Stokes syndrome, Surgery 52:765, 1962.
10. Elmqvist, R., and Senning A. An implantable pacemaker for the heart, Proc. Sec. Int. Conf. Med. El., London, 1960, Iliffe and Sons, p. 253
11. Chardack, W M., Gage, A. A., and Greatbatch, W A transistorized self contained, implantable pacemaker for the long-term correction of complete heart block, Surgery 48:643 1960.
12. Zoll, P M., and Linenthal, A. J Long-term electrical pacemakers for Stokes-Adams disease, Circulation 20:341 1960.
13. Kantrowitz, A., Cohen, R., Raillard, H., and Schmidt, J Experimental and clinical experience with new implantable cardiac pacemaker Circulation 24:967 1961.
14. Berg, J van den, Homan van der Heide, J N Nieveen, J Boonstra, E., and Kramer D.: An implantable transistorized pacemaker for the human heart with two years and control of the resistance of the tissues, the electrodes and the pacemaker Proc. Kon. Ned. Ac. Wet. 65:407 1962.
15. Davies, J G.. Artificial cardiac pacemakers for the long-term treatment of heart block, J Brit. I R. E. 24:453, 1962.
16. Thalen, H. J T Berg, J van den, Homan van der Heide, J N and Nieveen, J.: The artificial cardiac pacemaker Its history development and

2 to 4 postoperative days, probably because of a better fixation of the electrode within or against the cardiac tissue [39, 44] It should be noted that fibrous tissue and myocardium have a specific resistance within the same range of 150 to 300 ohms per centimeter The threshold rise is independent of electrical stimulation and is also recorded at spare electrodes. The tissue reaction seems to be a reaction to a foreign body in the myocardium and one factor that determines it is the rigidity of the electrode.

Infection around the electrode some time after implantation causes the same effect whereby the resistance of the electrode circuit is not influenced by the inflammatory process.[14] The resistance of the electrode circuit is composed of the internal resistance of the pacemaker output circuit the resistance of the electrode leads, electrode tissue between the electrodes and the complicated resistance at the transition between electrode and tissue. This last resistance can be differentiated in an ohmic resistance inversity proportional to the surface area of the electrode and effective resistance caused by a back electromotive force (EMF) due to polarization Polarization is a kinetic electrochemical process and a rather energy-consuming component in cardiac stimulation It is related to current electrode surface area time during which the current passes through the tissue and electrode material For our platinum iridium 10 per cent intramural loop electrode with 2 msec. impulse of 8 mA a polarization voltage of 1 1 v has been measured [14] This means that about 15 to 25 per cent of the voltage applied by the pacemaker to the heart or the energy of about one pacemaker battery is lost in polarization The same has been recorded by Greatbatch [41] who found that, of all metals tested platinum iridium and pure platinum gave the best combination of electrical stability and polarization losses, whereas Elgiloy and stainless steel have a higher polarization voltage and therefore poorer efficiency The poor electrochemical stability of stainless steel has even resulted in electrolysis in cases wherein this metal had been used for the indifferent electrode.[42] Besides electrochemical stability electrodes—and especially myocardial electrodes—need mechanical stability and elasticity As pure platinum is too weak the alloy platinum-iridium 10 per cent is used for the electrode proper whereas stainless steel and Elgiloy with their poorer electrochemical but greater mechanical stability are used for the electrode lead

Experience in cardiac stimulation resulted in more sophisticated and better pacemakers. Pacemaker lifetime remained restricted however to component reliability and pacemaker energy In 1964 Glass[43] calculated an over all component failure rate of 0 1 per cent per 1 000 hours. This means that one out of every 100 pacemakers would fail in 10 000 hours of stimulation At present this percentage has decreased because of improved components and isolation material [44]

Power supply still poses a limiting factor in cardiac pacing The mercury cells applied with the first implanted pacemaker are still in use These batteries of about 3 cm ^{3} and a weight of 12 to 12 5 Gm. contain mercury oxide and zinc as their active components. With a shelf life of 10 years, the initial capacity of these batteries is 1 000 mAh which is reduced by 7 per cent a year at body temperature.[45] This means a 30 per cent energy reduction after 4 to 5 years. The initial predictions of pacemaker lifetime of 5 years perhaps did not incorporate this reduction and were too optimistic. It is now accepted that implanted pacemakers generally function for periods ranging between 1 5 and 3 years. Improvements of the mercury cells have been made but periods of 5 years seem up to now not to be within the reach of this type of battery

Other power supplies have been investigated for instance conversion of mechanical energy into electrical energy by way of piezoelectrical ceramic crystals using diaphragm and rib movements or aortic pressure variations.[46] The experimental stage has never been passed Better results were obtained by using biogalvanic energy discs of two different metals are implanted in the body e.g at the pacemaker wall and the body fluid is used as electrolyte.[47] Pacemakers of this type using zinc and silver chloride or aluminum and silver chloride have been applied clinically but so far the

Clinical communications

Hypersecretion of estrogen in Takayasu's disease

Fujio Numano, M.D.
Takio Shimamoto, M.D.
Tokyo, Japan

Takayasu's disease is known to affect predominantly the aortic arch and its proximal branches.[1-7] It also affects other parts of the aorta and its branches, but the peripheral arterial system is usually free of this morbid condition. Apparently those portions of the arterial system that are exposed to the strongest mechanical stress from the cardiac stroke are most commonly affected. Another characteristic of this condition is the frequency of its occurrence in young women.[4-] However, the cause of the disease is unknown.

In the authors' experimental study, long-term treatment of rabbits with estrogen produced a striking atrophy of muscular layers in arteries and at the same time necrosis, calcification, and local nonspecific inflammatory reaction in the aorta,[8-11] simulating Takayasu's disease.[12-]

Such experimental evidence prompted us to analyze hormonal aspects of the disease; we concentrated on the abnormal urinary output of total estrogens in patients suffering from Takayasu's disease.

Materials and methods

Subjects of the present research were 20 female patients (aged 18 to 45 years, mean 32.2 ± 7.8 years) who had Takayasu's disease with the typical aortic arch syndrome, characterized by absence or weakness of pulse in the upper extremities due to arterial occlusion, and who showed some of the following symptoms: vertigo, headache, syncope, transient visual disturbance, and other ocular signs. In all patients aortography by catheterization confirmed the diagnosis. None showed abnormality in serum bilirubin, transaminases, alkaline phosphatase, or in liver function tests such as cephalin flocculation, bromsulphalein retention, thymol turbidity, and zinc turbidity. Patients showing appreciable abnormality in liver function were excluded from this experiment. Subjects were also certified as having had no hormonal therapy in their histories. Eighteen healthy women (aged 18 to 45 years, mean 31.8 ± 6.8 years) were used as control subjects. All test subjects underwent routine clinical and laboratory examination at the university hospitals.

Collection of urine for a 24 hour period was carried out on the seventh day after the onset of menstruation and on the seventh day before menstruation, in order to sample it during the follicular and luteal periods of the menstrual cycle. These samples were frozen immediately, stored at −20° C, and examined within a few days after collection. Urinary total estrogens were extracted by the method of Cohen[17] and Brown[18] modified by Nishi, and measured fluorometrically with the Shimazu UMS Microfluorophotometer.

Estrone (produced by Merck & Co.) was

From the Institute for Cardiovascular Diseases, Tokyo Ika-Shika National University Medical School, Yushima-1, Bunkyo-ku, Tokyo, Japan.
Received for publication June 1, 1970.

clinical application Assen The Netherlands, 1969 Van Gorcum Publ

17 Nathan D A Center S Chang You Wu and Keller W An implantable synchronous pacemaker for the long term correction of complete heart block Amer J Cardiol 11:362 1963

18 Sowton G E Haemodynamic studies in patient with artificial pacemakers, Brit. Heart J 26 737 1964

19 Bonnabeau R. C Wingrove R. Bilgutay A M Sterns, L. I and Lillehei, C. W A small implantable P wave pacemaker with no atrial electrodes needed Proc Nat. Biomed Sc. Instrum Symp 107: 1963

20 Chardack W M Ishikawa H Fochler F J Souther S and Gage A A Pacing and ventricular fibrillation Ann. New York Acad Sci. 167:919 1969

21 Donato L. and Denoth F Self synchronizing cardiac pacemaker for treatment of intermittent A V block Lancet 2:233 1966.

22 Leatham A Cook, P and Davies J G External electric stimulator for treatment of ventricular standstill Lancet 1185 1956.

23 Sykosch H J Effert S Pulver K G and Zacouto F Zur Therapie mit elektrischen Schrittmachern. Ein implantierbarer induktiv au schaltbarer elektrischer Schrittmacher Elektromedizin 8:139 1963

24 Fischer H Barr I M Auerbach A Yerushalmi S and Neufeld H N Atrial synchronized demand heart pacing I E. E E 61:16 1969

25 Sykosch H J Berkovits, B and M rs, E. Experiences with bifocal atrioventricular demand pacing *in* Symposium o cl nical a pects of long tern cardia pacing Monaco, 1970

26. Thalen H J T nd Berg J van den The R wave blocked pacemaker *in* Proc Vth Eur Congr of Cardiology Athens, 1968

27 Nieveen, J Berg J en den H man van der Heide, J N and Thalen H J T The pacemaker clinic *in* Symposium on linical spects of long term cardiac pacing Monaco 1970

28 Symposium on clinical aspect of lo g term cardiac pacing Monaco 1970

29 Toresann J *In* Symposium cardiac paci g VI World Congress of Cardiology Lond n, 1970.

30 Lagergren H Johansson L. Ka lof I and Thornander H Atrial triggered pacemaking without thoracotomy apparatus and results in twenty cases, Acta Chir Scand 132:678 1966.

31 Sowton E and Barr I Physiological hanges in threshold Ann. New York Acad Sci. 167:679 1969

32. Preston T A. and Judge, R. D Alteration of pacemaker threshold by drug and physiological factors, Ann. New York Acad. Sci. 167:686 1969

33 Hoffman B F and Cranefield, P F Electrophysiology of the heart New York, 1960, McGraw Hill Book Company Inc.

34 Dekker E. Thresholds to make and break direct current in pacemaker electrodes on the canine ventricle *in* VI World Congress of Cardiology abstracts of papers, Cardiovasc. Res. 118, 1970

35 Angelakos, E. T and Torres, J C. The efficiency of electrical pulses for cardiac stimulation Cardiologia 44:355 1964

36. Siddons, H., and Sowton, E. Cardiac pacemakers, Springfield Ill., 1967 Charles C Thomas, Publisher

37 Preston T A. Judge R. D Bowers, D L and Morris, J D: Measurement of pacemaker performance AMER. HEART J 71:92, 1966.

38. Berg J van den and Thalen, H J T Internal pacemaker with external control of the stimulation threshold of the heart Proc. Kon. Ned. Wet 0:448, 1967

39 Thalen, H J T Clinical experience with the threshold pacemaker Meeting English-Dutch Society of Cardiology Amsterdam, 1970.

40. Fontaine G Discussion and remarks *in* Congress on clinical aspects of long-term cardiac pacing Monaco, 1970.

41 Greatbatch W Electrochemical polarization of physiological electrodes, Med. Res. Eng 6 1967

42 Rowley B A. Electrolysis. A factor in cardiac pacemaker electrode failure, I E. E. E. 10:176, 1963

43 Glass, H I Problems associated with the design of implantable electronic devices, *in* Proceedings of the congress on resuscitation and cardiac pacing London, 1970 Cassell & Co Ltd p. 207

44 Dodinot B I Entraînement électrosystolique synchrone Ac. Thesis, Nancy 1967

45 Ruben S. Sealed zinc mercuric oxide cells for implantable cardiac pacemakers, Ann. New York Acad Sci. 167:627 1969

46. Parsonnet V Meyers, G. Zucker E. R., and Lotman H The potentiality of the use of biologic energy as a power source for implantable pacemakers, Ann. New York Acad. Sci. 111:915 1964

47 Schaldach M Ei elektrochemisch betriebener Herzschrittmacher Wiederbelebung und Organersatz, 5:75 1968.

48 Laurens, P Mals, M Berger R. Boucher R., Mulser P nd Piwnica A. Nuclear po ered pacemakers, *in* Symposium on clinical aspects of long term cardiac pacing Monaco, 1970.

49 Poole, M J and Sowton, E. The U K. program for the development and evaluation of a nuclear powered pacemaker *in* Symposium on clinical aspects of long term cardiac pacing M naco, 1970

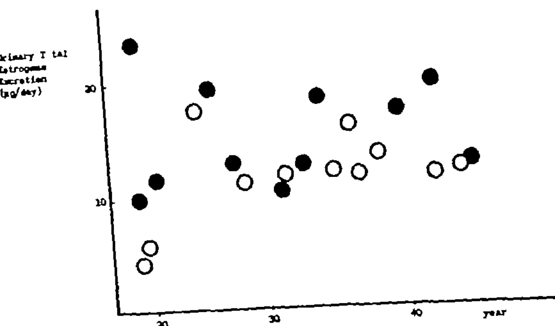


Fig. 2. Total urinary estrogen excretion during the luteal period.

Table I. Urinary total estrogens, 17-OHCS and 17 KS excretion in normal subjects and in patients with Takayasu's disease

Group	Total urinary estrogen excretions (µg/day)		Total 17-OHCS excretions (mg./day)	Total 17 KS excretions (mg./day)
	Follicular phase	Luteal phase		
Normal subjects	7.4 ± 0.8	10.7 ± 0.9	5.6 ± 0.5	5.6 ± 0.7
Takayasu disease	13.7 ± 1.4	11.7 ± 1.2	4.5 ± 0.4	3.6 ± 0.6

*p < 0.01.

This was higher than in normal subjects but the difference between the groups was not statistically significant.

The excretion of total 17-OHCS and 17 KS in urine was within normal limits in all subjects of both groups, as shown in Table I.

Two patients with Takayasu's disease, aged 27 and 32, exhibited relatively profuse menstrual bleeding, and two others, aged 23 and 44, exhibited relatively prolonged menstrual bleeding. However, there was no appreciable change in the menstruation of the other subjects. No other hormonal abnormality was noted.

Discussion

As shown by Cohen[17] and Brown,[18] the urinary excretion of total estrogens in mature women commonly diminishes in the follicular period and rises in the luteal period. Our results with healthy women exhibited the same biphasic pattern and almost the same values for hormone excretion in the respective periods as those reported by Brown and Bauld.[18,24]

On the other hand, the biphasic pattern of the urinary excretion of total estrogens was entirely absent in patients with Takayasu's disease. Estrogen excretion in the follicular period exhibited no decline but

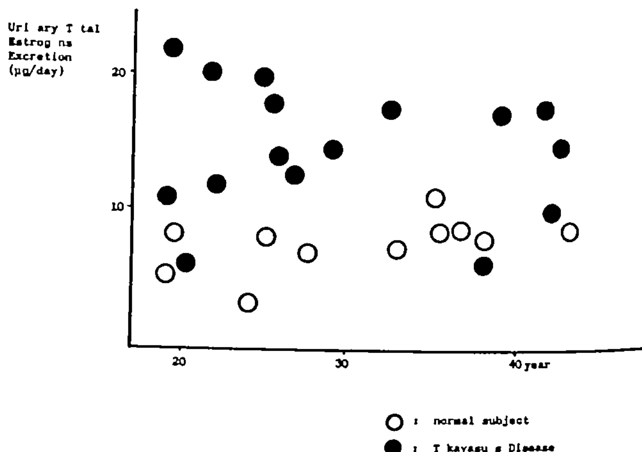


Fig 1 Total urinary estrogen excretion during the follicular period.

used as a standard and total urinary estrogen excretion was calculated as total estrone excretion Optical densities were measured at the three wavelengths of 460 480 and 500 mμ with an excitation wave length of 435 mμ and corrected for non specific absorption by the method of Allen [20] At the same time urinary total 17 ketosteroids (17 KS) were measured according to the method of Rappaport Ischl and Pinto [21] and urinary total 17 hydroxy corticosteroids (17-OHCS) by the method of Porter and Silber[22] modified by Nishikaze

Results

Urinary total estrogen excretion during the follicular period The urinary excretion of total estrogens during the follicular period were analyzed in 11 normal subjects and in 16 patients with Takayasu s disease The quantities obtained in the study of normal subjects were low ranging below 10 μg per day (mean value, 7 4 ± 0 8 μg per day) On the other hand as indicated in Fig 1 it appeared likely that the urinary excretion of total estrogens in women with Takayasu s disease is increased as compared with that of normal subjects. These patients excreted 13 7 ± 1 4 μg per day of total estrogens on the average and there was a statistically significant difference between these values and those of the control group ($p < 0.01$) It is highly interesting that the younger group of patients, i e those of 18 20 and 26 years, excreted four or five times as much estrogen in the urine as those of the same age among normal subjects (shown in Fig 1)

Urinary excretion of total estrogens during the luteal period The urinary excretion of total estrogens was measured in 11 normal subjects and 11 patients with Takayasu s disease during the luteal period There was a progressive increase of urinary excretions in normal subjects. They excreted 10 7 ± 0 9 μg per day of estrogens on the average. Meanwhile as shown in Fig 2 and Table I urinary excretion of total estrogens in patients with Takayasu s disease also exhibited a high value, 12 7 ± 1.2 μg per day

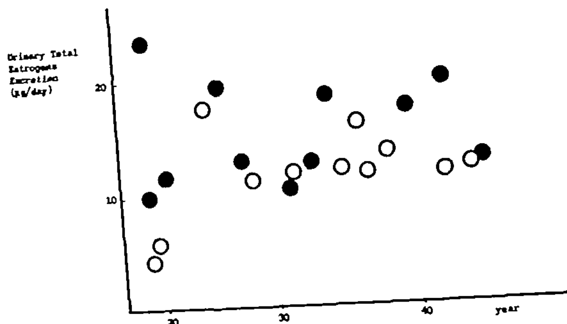


Fig. 2. Total urinary estrogen excretion during the luteal period.

Table I. Urinary total estrogens 17-OHCS and 17 KS excretion in normal subjects and in patients with Takayasu's disease

Group	*Total urinary estrogen excretions (µg/day)*		*Total 17-OHCS excretions (mg./day)*	*Total 17 KS excretions (mg./day)*
	Follicular phase	*Luteal phase*		
Normal subjects	7 4 ± 0 8	10 7 ± 0 9	5 6 ± 0 5	5 6 ± 0 7
Takayasu disease	13 7 ± 1 4	12 7 ± 1 2	4 5 ± 0 4	3 6 ± 0 6

*p 0 01.

This was higher than in normal subjects but the difference between the groups was not statistically significant.

The excretion of total 17-OHCS and 17 KS in urine was within normal limits in all subjects of both groups, as shown in Table I.

Two patients with Takayasu's disease, aged 27 and 32 exhibited relatively profuse menstrual bleeding, and two others, aged 25 and 44 exhibited relatively prolonged menstrual bleeding. However there was no appreciable change in the menstruation of the other subjects. No other hormonal abnormality was noted.

Discussion

As shown by Cohen[17] and Brown,[18] the urinary excretion of total estrogens in mature women commonly diminishes in the follicular period and rises in the luteal period. Our results with healthy women exhibited the same biphasic pattern and almost the same values for hormone excretion in the respective periods as those reported by Brown and Bauld.[18,24]

On the other hand the biphasic pattern of the urinary excretion of total estrogens was entirely absent in patients with Takayasu's disease. Estrogen excretion in the

remained significantly high (almost equal to the excretion level in the luteal period) The values in the luteal period were relatively high although the difference between the patients and the controls in the luteal period was not statistically significant. This result may suggest that the patient with Takayasu's disease often has an anovulatory menstruation In fact in our recent analysis with gas chromatography the decreased urinary excretion of pregnanediol suggesting an anovulatory menstruation was often encountered in these patients and an investigation is now under way At any rate there is evidence to suggest the production of estrogens at a high level throughout the menstrual cycle in patients with Takayasu's disease

As shown in our experimental study on rabbits[9,10] long term treatment with estrogen produced a striking atrophy of muscular layers, necrosis, calcification and nonspecific inflammatory response of the aorta, closely resembling Takayasu's disease Among such pathologic symptoms the striking atrophy of muscular layers deserves attention because the arterial changes were predominantly localized in the parts of the aorta and its branches under the strongest mechanical stress from the arterial blood stream and pulsation Such evidence suggests the continuous high level of estrogen production as a cause of Takayasu's disease

There have been many hypotheses as to the cause of Takayasu's disease For instance Shimizu and Sano[26] considered that Takayasu's disease may be thrombo-arteritis obliterans due to tuberculosis. This has been negated by many authors however a high incidence of tuberculosis in the histories of patients with Takayasu's disease has been known in Japan[7] and also in India[18] Recently a certain immune process was postulated by Ueda and associates[17,18] and by Ikeda[19] The latter reported a positive antiglobulin reaction by tanned red cells in seven out of nine cases of Takayasu's disease and the former group reported a high incidence of antiaorta antibodies. However they also reported a relatively high incidence of such antibodies in other diseases, such as renovascular hypertension.[18-20]

In contrast Wakisaka and co-workers[22] and Hirsch Alkat and Basu[24] reported negative circulating antibodies against human aorta Immunobiological analysis by Walton[23] also revealed negative results in patients with Takayasu's disease. Ueda and co-workers[17,18] and Saito[21] interpreted their positive results as inconclusive in determining whether the antigen-antibody reaction is the cause or the result of aortic changes. Also the characteristic localization of arterial changes in Takayasu's disease is difficult to understand as the result of a general antigen antibody reaction the antigen of which has been extracted from arterial tissue.

On the other hand the hypersecretion of estrogen found in the present investigation may well account for the characteristic localization of lesions in the arterial system. It is widely known that large doses of estrogen frequently damage the vessel wall. The Veterans Administration Co-operative Urological Research Group's study[27] exhibited the increased risk of death from cerebrovascular accidents and cardiovascular diseases in the patients with prostatic cancer treated with high doses of estrogen. Recently the complication of vascular lesions associated with thrombosis has been focused upon women taking oral contraceptives. Irey Manion and Taylor[28] reported that their pathologic study revealed that the three-layered thrombi and the underlying structural and histochemical changes in the vessel wall were found in 19 out of 20 women taking oral contraceptives. It may be postulated that the aorta and its direct branches, exposed to strong mechanical stress from cardiac stroke, are specifically damaged in such circumstances. In fact, the onset of this morbid condition is generally thought to be early in puberty when hormonal imbalance is most remarkable and the growth of the body including the blood vessels is still going on even if the clinical symptoms appeared in the third or fourth decade of life Furthermore, some form of malnutrition especially among women of the Far East or tuberculosis[29] may be considered as other factors inducing the general atrophy of arteries and the lowering of resistance to stress. The combination of such nutritional factors and the

above-mentioned hormonal factor may account for the high incidence of Takayasu's disease in the Far East, especially among women with histories of tuberculosis.

In our experimental studies with rhesus monkeys and rabbits, estrogens such as Premarin or diethylstilbestrol significantly reduced the activity of glycolytic enzymes on the arterial wall.[14] Such effects may be involved in the atrophy of arterial smooth muscles induced by estrogens and may be a contributing factor in Takayasu's disease, although further analysis of hormonal as well as enzymatic aspects of Takayasu's disease is required.

Summary

The 24 hour urinary excretion of total estrogens was measured by the methods of Cohen,[17] Brown,[18] and Nishi in 20 healthy women aged 18 to 45 (mean 31.8 ± 6.8) and in 20 patients with typical Takayasu's disease aged 18 to 45 (mean 32.2 ± 7.8) during the follicular and luteal periods, respectively. A continuous high level of urinary excretion of total estrogens without normal biphasic rhythm was found in those with Takayasu's disease. The 24 hour urinary excretion of total estrogens during the follicular period was 7.4 ± 0.8 μg per day in the control subjects and 13.7 ± 1.4 μg per day in the patients; the difference was statistically significant ($p < 0.01$). During the luteal period the excretion was 10.7 ± 0.9 μg per day in the control subjects and 12.7 ± 1.2 μg per day in the patients.

The continuous high level of urinary excretion of total estrogens found in this study has been discussed as one possible explanation of the characteristic localization of this morbid condition in the arterial system.

REFERENCES

1. Caccamise, W. C., and Whitman, J. F.: Pulseless disease, Amer. Heart J. 44:629, 1952.
2. Judge, R. D., Currier, R. D., Gracie, W. A., and Figley, M. M.: Takayasu's arteritis and the aortic arch syndrome, Amer. J. Med. 32:379, 1962.
3. Ross, R. S., and McKusick, V. A.: Aortic arch syndromes, Arch. Intern. Med. (Chicago) 92:701, 1953.
4. Frövig, A. G.: Bilateral obliteration of the common carotid artery, Acta Psychiat. Neurol. (Suppl.) 39, 1946.
5. Bergbon, J. D.: Les arteriopathies de type Takayasu, Beaux-arts, Lyon, 1969.
6. Boström, K., and Hassler, O.: Takayasu disease, post-mortem examination of a previously published case, Acta Med. Scand. 178:537, 1965.
7. Committee report: Clinical and pathological studies of aortitis syndrome, Jap. Heart J. 9:76, 1968.
8. Shimamoto, T.: Experimental study of atherosclerosis—An attempt at its prevention and treatment, Acta Path. Jap. 19:15, 1969.
9. Numano, F., Kitta, T., Katsu, K., and Shimamoto, T.: A comparison on preventive effect of estrogens and pyridinolcarbamate against atherosclerosis of cholesterol-fed rabbits, J. Jap. Coll. Angiol. 10:33, 1970.
10. Numano, F., Katsu, K., Takenobu, M., and Shimamoto, T.: A comparison on prevention of estrogens and pyridinolcarbamate against cholesterol-induced atherosclerosis. I. Pathological and topographic study. II. Histoenzymatic study, Acta Path. Jap. 21:182, 1971.
11. Numano, F., Katsu, K., Takenobu, M., and Shimamoto, T.: Increased urinary excretion of total estrogens in Banti's and aortic arch syndrome, Jap. J. Clin. Med. 10:42, 1971.
12. Benecke, R., and Halle, A. S.: Ein eigentümlicher fallsichtweiliger Aortitis, Virchow Arch. Path. Anat. 254:723, 1925.
13. Harbatz, F.: Bilateral carotid arteritis, Arch. Path. (Chicago) 1:499, 1926.
14. Nasu, T.: Pathology of pulseless disease; a systematic study and critical review of twenty-one autopsy cases reported in Japan, Angiology 14:225, 1963.
15. Inanaka, T., Handa, A., Ohtsuka, R., Isaki, K., Tsubokawa, H., and Ohta, G.: An autopsy case of aortitis syndrome with extensive aortic calcification, aortic insufficiency, myocardial infarction and thromboembolic obstruction of basilar artery, Naika 22:772, 1968.
16. Pieris, E. V.: Extensive calcification of the aorta with coarctation secondary to Takayasu's disease, Ceylon Med. J. 14:28, 1969.
17. Cohen, S. L.: A method for the rapid colorimetric assay of total estrins in pregnancy urine, J. Clin. Endocr. 26:994, 1966.
18. Brown, J. B.: A chemical method for the determination of oestriol, oestrone and oestradiol in human urine, Biochem. J. 60:185, 1955.
19. Nishi, N.: Gas chromatography analysis of urinary pregnanediol, pregnanetriol and estrogens in pregnancy and in the patient treated with gonadotropin, J. Jap. Obstet. Gynec. Soc. 22:1013, 1970.
20. Allen, W. M.: A simple method for analyzing complicated absorption curves, of use in the colorimetric determination of urinary steroids, J. Clin. Endocr. 10:71, 1950.
21. Rappaport, F., Fischl, F., and Pinto, N.: A rapid method for the estimation of urinary 17-ketosteroids, Clin. Chem. 6:16, 1960.
22. Porter, C. C., and Silber, R. H.: A quantitative color reaction for cortisone and related 17,21-

dihydroxy 20-ketosteroids, J Biochem. (Tokyo) 185:201 1950.
23 Brown, J B Urinary excretion of oestrogens during the menstrual cycle, Lancet 1:320 1955
24. Bauld W S. A method for the determination of oestriol, oestrone, and oestradiol-17β in human urine by partition chromatography and colorimetric estimation, Biochem. J 63:483 1956
25. Shimizu K. and Sano K. Pulseless disease, J Neuropath. Exp. Neurol. 1:13 1951
26. Kinare, S G. Osteopathological aspects of non specific aortitis, Proc. Fourth Asian Pacific Congress of Cardiography Tel Aviv Sept. 4 1968.
27 Ueda H. Aortic arch syndrome and its etiology Nippon Rinsho 26:3300 1968.
28. Ueda H. et al. Immunological studies of aortitis syndrome Jap. Heart J 8:4 1967
29 Ikeda M Immunologic studies on Takayasu s arteritis, Jap. Circ. J 30:87 1966.
30. Ueda H Morooka, S. Ito, I., Yamauchi H Takeda, T., and Saito, T Clinical observation of 52 cases of aortitis syndrome Jap. Heart J 10:277 1969
31 Saito, Y : Immunological studies of aortitis syndrome—complement fixation test and precipitation test J Jap. Soc. Intern. Med. 56:441 1967
32 Ueda H : Renovascular hypertension as a manifestation of aortitis syndrome, Jap. Heart J 8:209 1967
33 Wakisaka G Nagata I Sawada, H., Tanegai, M Furusawa, H Kuramoto, K., Mitsutani, S. Tomie, K. Yamada K. Okuma, M., and Hibino, T : Two cases of pulseless disease, J Jap. Soc. Intern. Med. 53:893 1964.
34 Hirsch M S., Aikat B. K., and Basu, A. K. Takayasu s arteritis, report of 5 cases with immunologic studies, Johns Hopkins Med. J 115:29 1964.
35 Walton K. W Personal communication.
36. Ueda, H Saito, Y., Morooka S., Ito, I and Yamaguchi H Experimental arteritis produced immunologically in rabbits, Jap. Heart J 9:573 1968.
37 The Veterans Administration Co-operative Urological Research Group Treatment and survival of patients with cancer of the prostate, Surg Gynec. Obstet. 124:1011 1967
38. Irey N S. Manion W C., and Taylor H. B.: Vascular lesions in women taking oral contraceptives, Arch. Path (Chicago) 89:1 1970.
39 Kinare, S. G Aortitis in early life in India and its association with tuberculosis, J Path. Bact. 100:69 1970.

Serologic evidence of a sporadic outbreak in Illinois of infection by Chlamydia (psittacosis-LGV agent) in patients with primary myocardial disease and respiratory disease

George C. Sutton, M.S., M.D.
John A. Demakis, M.D.
Truman O. Anderson, Ph.D., M.D.
Richard A. Morrissey, M.P.H.
*With the Idiopathic Myocardial Disease Study Group of the Cook County Hospital**
Chicago, Ill.

There have been many reports linking chlamydial infection with disease of the perimyocardium since Adamy[1] first described this in 1930. The authors'[2] experience with nine serologically positive cases of acute chlamydial disease of the heart led to the deliberate search for serologic evidence of chlamydial infection among Illinois patients with primary perimyocardial disease (PMD) starting in 1961. Forty such patients (exclusive of those typical acute cases previously reported[2]) were detected predominantly in the years 1963 and 1964. Long-term observations of these 40 patients, including laboratory procedures (use of multiple chlamydial antigens, radioiodine precipitation test, and absence of reaction to chicken egg allantoic membrane per se, or as altered by Newcastle disease virus) designed to confirm the specificity of the complement-fixation (CF) method as an indicator of chlamydial infection, form the substance of this report. It is pertinent to point out that, although the greatest number of cases of psittacosis are reported from the Federal Republic of (West) Germany,[11] the United States ranks second. For many years Illinois, California, Texas, and Minnesota, have been the major sites of the disease[13,14] in this country. These infections have been attributed to contact with poultry, especially chickens, and perhaps wild pigeons. In 1953 Illinois had a marked increase in cases to 45 (highest in the nation) predominantly among rural

From the Department of Adult Cardiology of the Hektoen Institute of Medical Research of the Cook County Hospital; the Departments of Medicine of the Northwestern University School of Medicine, the Stritch School of Medicine of Loyola University, and the University of Illinois College of Medicine, and the Illinois Department of Public Health.

This investigation was supported in part by Grant RX-63-24 from the Chicago Heart Association, Grant HE-9666 from the National Heart Institute, United States Public Health Service, and the Public Laboratory Research Fund.
Received for publication June 1, 1970.

Reprint requests to: George C. Sutton, M.S., M.D., Adult Cardiology Section, Department of Medicine, Cook County Hospital, 1835 W. Harrison St., Chicago, Ill. 60612.
*John R. Tobin, Jr., M.D., Rolf M. Gunnar, M.D., Raymond J. Pietras, M.D., and M. Zaid Samra, M.D.

families in the northwestern section of the state

Again in the period 1961 to 1967 Illinois experienced a marked rise in the number of patients with significant serologic reaction to psittacosis lymphogranuloma venereum (LGV) agent (referred to hereafter as Chlamydia) which reached its peak in 1963 and 1964 Unlike the experience in 1953 this outbreak occurred largely among the urban population Of particular interest during this latter outbreak was the unusual frequency of serologic response to chlamydial agents among patients with primary myocardial disease (PMD) This observation suggested that infection by a chlamydial agent might be involved in the production of certain forms of PMD

Methods

Patient population The patient population was drawn from three sources (1) patients hospitalized with PMD studied within Cook County Hospital by the Idiopathic Myocardial Disease Study Group (2) patients with PMD hospitalized in other Illinois hospitals and referred to the IMD Study Group for study and (3) patients with noncardiac manifestations of chlamydial disease whose physicians submitted sera for viral antibody measurements to the Department of Public Health Viral Laboratories of the State of Illinois The patients thus identified were classified as shown in Table I In Series I 319 patients were subdivided into Group A (40 PMD patients with multiple significant CF titers against Chlamydia) and Group B (279 patients with PMD and no serologic evidence of chlamydial disease) Series II consisted of 245 patients with fever of unknown origin lymphogranuloma venereum upper respiratory illness, or pneumonitis and sera displaying significant CF antibody titers to Chlamydia This series was detected by study of 12 743 consecutive sera submitted for study to the State Laboratory (1961 1967) * Such a control group was considered to be the least biased by virtue of its selection from the general population thus consisting of persons most

* In 1961 routine serologic testing for chlamydial infection was included in the study of sera of all patients thought to have viral disease.

Table I Composition of Series I (study group) and Series II (control group)

Subdivision and characteristics	Subtotal	Total
Series I Patients with PMD		
Group A Patients with PMD and multiple sera reacting to chlamydial agent—29 Cook County Hospital patients and 11 in other Illinois hospitals	40	
Group B Patients with PMD and no serologic evidence of chlamydial disease	279	
Total		319
Series II Patients with noncardiac manifestations of chlamydial disease		245

Developed from study of 12,743 sera submitted to State of Illinois Viral Laboratories from 1961 to 1967

likely to have serologic evidence of infection The sera of 95 young patients with heart disease of known etiology (Cong RHD ASHD etc.) were also examined during these years as a secondary control population these are not included in Table I

The criteria employed to establish the diagnosis of chlamydial infection on a serologic basis were two or more sequential sera with titers of 1 16 or greater or a series of sera showing a fourfold decrease in titer from an initial level of 1 32 or greater Continued serologic study was sought in all patients.

The term PMD is employed in the context of disease affecting the perimyocardium per se including diseases of recognized etiologies (such as cobaltous or viral PMD) as well as disease of obscure etiology (termed idiopathic PMD) The criteria used to establish the diagnosis of PMD were uniform in both groups of Series I and were those described in previous publications.[9, 15, 16]

Characterization of Series I patients Data recording and processing throughout the course of this study on PMD were facilitated by the use of a computer program. The specific data are shown in Table II In selected instances, exploratory mediastinotomy with coronary artery visualiza

Table II. Specific elements of data recorded by use of a computer program in characterizing Series I patients with PMD

History: Family disease, race, vector contact, environment, occupation, locale of residence, associated noncardiac infectious disease, associated heart disease (congenital, rheumatic, arteriosclerotic, luetic, viral, alcoholic, etc.) nutritional habits, obstetrical history past and presenting illness

Physical examination. Complete physical examination, evidence of pleural, pulmonary pericardial, myocardial, or urogenital disease. Cardiac examination, blood pressure, venous waves, hemodynamic status, ventricular hypertrophy character of S_{1-4}, systolic or diastolic sounds or murmurs

Cardiac diagnostic procedures. Two-meter PA and lateral chest x-rays, cardiac fluoroscopy serial 12 Lead electrocardiograms (ECG) (New York Heart Association classification) Frank system vectorcardiograms (VCG) (criteria of Hugenholtz and associates[17])

Ancillary laboratory procedures: Kahn, complete blood count (CBC) antistreptolysin-O (ASO) titer urinalysis, blood sugar cholesterol, serum glutamic oxalacetic transaminase (SGOT) thymol turbidity cephalin flocculation, total protein, hemoglobin (Hb) electrophoresis, venous pressure, circulation time, lupus erythematosus (LE) cells

Spectrum of test antigens employed. Mumps (soluble) poliomyelitis, herpes simplex, adenovirus, Q fever influenza A and B, parainfluenza 1, 2, and 3, *Mycoplasma pneumoniae*, respiratory syncytial virus, Coxsackie B Chlamydia.

tion and palpation and with transmural ventricular myocardial biopsy was done (10 patients) Coronary arteriography was performed successfully in seven patients, utilizing aortic root flooding in six, and selective coronary artery injection in one case.

SEROLOGIC STUDIES. 1 Serial CF tests were performed. Prior to testing all the sera were stored at −5° C Serial CF tests for specific antibodies were done at one to three-month intervals initially by the microtechnique, subsequently by the microtiter method The spectrum of test antigens is listed in Table II Although as a routine all tests for Chlamydia were done with Psittacosis Human Diagnostic Antigen (Markham Laboratories, Chicago, Ill) representative serum specimens were cross checked periodically with other psittacosis antigens Psittacosis complement fixation antigen (Cat. No. 75-0231) CDC, and Psittacosis Diagnostic Antigen, Rocky Mountain Laboratory (CDC)

2 In addition 49 samples of serum from 12 patients who had displayed persistent CF antibody titers to Chlamydia were also evaluated by the radioisotope precipitin test (RIP) for Chlamydia group antibody [8] This test was performed by Dr R. K. Gerloff (Rocky Mountain Laboratory United States Public Health Service)

3 Simultaneous complement-fixation tests were carried out as follows. In the spring of 1967 using the microtiter modification of the CDC laboratory branch complement-fixation test, sequential serum specimens (three or more) from eight patients with PMD of Group A were restudied for complement fixing antibody titers to the following antigens herpes simplex, herpes simplex control influenza A and B (soluble) mumps (soluble and viral) chorioallantoic membrane control psittacosis, psittacosis host tissue (uninfected) adenovirus, adenovirus (tissue) control Coxsackie virus types B_{1-6}, and Coxsackie virus host tissue (uninfected) Serum control spanning dilutions from 1/2 to 1/256 were included for each specimen tested.

Characterization of Series II patients Based on the same serologic criteria and stemming from the study of 12 743 sera from the State of Illinois Viral Laboratory (1961 to 1967) a second series of 245 patients whose sera reacted positively to Chlamydia was collected by two of us during the same years (1961 to 1967) None had PMD Among these patients were found (1) significant CF antibody to Chlamydia agent, (2) no evidence of cardiac disease, and (3) clinical evidence of a disease attributable to chlamydial infection, i.e. fever of unknown origin lymphogranuloma venereum, respiratory disease, or pneumonia. Their final clinical classification in the present study was based solely on written data furnished by their private physicians utilizing the facilities of the State Laboratory as an aid in the diagnosis

Table III Frequency of occurrence of associated cardiac disease and of physical radiologic, and electrocardiographic abnormalities of perimyocardial disease in 40 PMD patients (Group A) with serologic evidence of chlamydial infection

	Type of associated disease			
	Alcoholic PMD	Viral PMD	Postpartum PMD	Rheumatic or arteriosclerotic heart disease
No of patients	14	19	3	4
Pericarditis, rub or effusion	0	11	0	1
Cardiomegaly by x ray	11	4	3	3
Ventricular gallop S_3	10	6	2	2
Atrial gallop S	11	7	2	0
Coronary arteriograms				
No defects	2	1	0	1
Minor defects	1	1	0	0
No tested	3	2	0	1
ECG and VCG abnormalities				
Rhythm disturbances	1	0	1	1
Hypertrophy with ST T changes	11	5	2	1
IV conduction disturbances	1	1	0	0
Isolated ischemic ST T abnormalities	5	13	1	2
Infarct patterns	5	3	1	2

of their patients The number of sera examined for antibody to Chlamydia agent and the number displaying significant titer of CF antibody to Chlamydia are shown by years in Table VII

Results

Clinical studies (Series I) Among the 319 patients with PMD 40 (Subgroup A) had laboratory evidence of infection by Chlamydia agent and 279 (Subgroup B) had no such evidence (Table I) Comparison of data on the patients revealed a similar broad spread of age and a predominance of nonwhite (Negro) males. In the group of 40 Chlamydia reactors 17 had parakeet, canary pheasant or pigeon contact three had dog contact one patient had direct contact (kissing) with a human being hospitalized with psittacosis One patient snared and ate robins and became very ill

The prevalence of additional intercurrent, cardiac disease was similar in both groups of patients with PMD The predominant form was either alcoholic heart disease without hepatic involvement (Subgroup A 35 per cent Subgroup B 37 per cent) or acute viral cardiac disease (Subgroup A 48 per cent Subgroup B 22 per cent) It was not possible to distinguish on historical clinical or laboratory bases, among patients with alcoholic heart disease, those who did from those who did not display antibody to Chlamydia The case was analogous in other types of PMD Four patients of Subgroup A also had clinical evidence of either coronary atherosclerosis (one) or rheumatic heart disease (three)

Clinical data pertinent to the cardiac disease associated with serologic evidence of Chlamydia disease is presented in Table III The presence of pericarditis, cardiomegaly and ventricular and atrial gallop sounds as well as ECG and VCG abnormalities was appropriate to the type of PMD A statistical comparison of attributes of each type of associated disease was not feasible numerically

Serial ECG s and VCG s in the patients of Series I displayed changing patterns the abnormalities listed represent the most severe changes seen in the course of the

disease. Patterns compatible with infarct were seen at some time in 11 patients who ranged in age from 21 to 51 years (mean 39 years) Absence of coronary disease at a later date was demonstrated by postmortem examination (one) by coronary angiogram (three) and by exploratory mediastinotomy (two) in 6 of these 11 patients with infarct patterns. Ancillary laboratory procedures revealed an absence of complicating noncardiac disease with the exception of one case— that of a 29-year-old alcoholic heroin addict with positive VDRL, positive FTA, and alcoholic PMD without evidence of luetic cardiovascular disease

Surgical and histologic studies Surgical exploration of the mediastinum and transmural ventricular biopsy with palpation of the coronary arteries and inspection of the anterior wall (Table IV) was performed[18] in ten patients of Subgroup A (six alcoholic and four viral) No significant pericardial or coronary disease was found in any of the ten. Histologic evaluation of the myocardial tissues obtained by biopsy and examined by light microscopy showed diffuse fibrosis, with and/or without myocardial hypertrophy in four patients. Nonspecific myocarditis was present in four; in two the myocardium was normal The data obtained by biopsy were supplemented by postmortem examination of the heart of two additional patients. One showed myocardial hypertrophy and normal coronary arteries the second showed diffuse myofibrosis and mild coronary atheroma.

The duration of longitudinal studies of 40 PMD patients reacting to Chlamydia and their clinical and serologic status at the time of last observation are presented in Table V Eight have died of cardiovascular causes 32 are living Of these 32 18 are symptom free and the remaining 14 exhibit chronic heart failure. All 32 surviving patients have ECG or radiographic stigmas of cardiac involvement. Twenty-three of the surviving patients have continued to display persistent serologic evidence of Chlamydia infection during the entire period of observation.

Serologic studies (Table VI) Fluctuating CF antibody titers to adenovirus, herpes simplex, and Influenza A have been observed in sequential sera from several of the

Table IV Results of surgical and postmortem examination of the heart in 12 patients with PMD and with serologic evidence of chlamydial infection

Method and findings	*No. of patients*
Exploratory mediastinotomy with myocardial biopsy	10
Coronary artery palpation	
Normal	9
Slight beading	1
Myocardial histology from biopsy	
Hypertrophy/fibrosis	2
Myofibrosis	2
Myocarditis	4
Normal myocardium	2
Post mortem	2
Myocardial hypertrophy/fibrosis, normal coronary arteries	1
Diffuse myofibrosis, mild coronary atheroma	1

Series I patients. Only one patient of the eight whose sequential sera were tested simultaneously displayed a rise in titer to other viral agents (adenovirus) and none reacted to tissue control antigens. None of the five sera displaying titers of 1:32 to 1:128 to Chlamydia reacted to the Newcastle disease virus system the sera of two patients with prior tuberculous pericarditis were also nonreactive. None of the seven sera displaying titers of 1:16 to 1:256 to chlamydial agent showed any titers to Coxsackie B_{1-6}. In test Item No 2 Table VI presents the maximum titer obtained by simultaneous testing of serum specimens. In test item No 3 the maximum titer represents the highest antibody level detected in the course of isolated specimen evaluation using a standard reference serum rather than a paired serum control. The disparity of maximum titer in items Nos. 2 and 3 is traceable to either (1) the fact that identical sera were not available for testing in the two series, or (2) variability in the test reagents employed

Forty-eight of 49 sera (test Item No. 1) from nine patients (Nos. 24 30 34 59 60 73, 80 and 19) had corrected P

Table V Longitudinal studies of 40 PMD patients (Group A) with serologic reactivity to chlamydial agent Duration of observation deaths clinical status and number of patients showing persistent serologic evidence of chlamydial infection at end of period of observation

Period of observation (mo)	No of patients	Clinical status at end of period			No. of patients with reactive sera at end of observation
		Dead	Well	Ill	
< 12	9	—	9	1	7
12-24	3	2	—	1	3
24-36	3	1	1	1	1
36-48	7	2	2	3	5
48-60	7	1	2	3	4
60 or >	11	2	4	5	3
Total	40	8	18	14	23

values * *above* 20 when subjected to the radioisotope precipitation test (RIP)[18] This term P value * equals the percentage of radioactivity of meningoencephalitis elementary *bodies* labeled with P^{32} precipitated by the test serum normal limits of P are −20 through +20 While 48 of 49 sera had abnormal values (>20) seven of the nine patients had sera with grossly abnormal values of 60 or higher similar to the levels of patients observed by Gerloff and Watson[20]

Epidemiologic studies The comparative epidemiologic data are presented in Table VII The yearly number of sera examined by the State of Illinois Laboratories for antibody to Chlamydia has fluctuated from about 1 600 to ? 600 in these seven years The number of noncardiac patients with significant CF antibody titers rose to a peak of 72 in 1963 and slowly decreased to six in 1967 The IMD Study Group began functioning in 1961 seeing 28 patients with PMD The number of new patients detected annually peaked at 76 in 1963 but continued at levels between 30 and 60 new patients each year The number of patients with PMD and significant antibody to Chlamydia rose abruptly to a peak of 19 or 25 per cent in 1963 and had declined markedly in face of a continuing high number of sera submitted for study and a continuing number of new patients detected with PMD in subsequent years.

Series II The number of patients whose sera was submitted to the State of Illinois Viral Laboratories for examination for Chlamydia antibody and the number and per cent displaying CF antibody to Chlamydia are presented by years in Table VII The years of peak incidence (3.3 per cent) of noncardiac chlamydial disease were 1962 and 1963 Eighty of 95 patients with cardiac disease of known cause had serial sera which did not react with *viral* antigens (adenovirus influenza A_1 Coxsackie B) and were not anticomplementary Only two of these 80 (2 5 per cent) had serial CF titers to Chlamydia of 1 16 none showed a fourfold decline from higher titer These significant titers were interestingly observed in 1963

Discussion

This report deals with epidemiologic observations of chlamydial disease made in a localized geographic area, i.e. northern Illinois, during a limited time span There is great seasonal and annual variation in the appearance of chlamydial disease in any particular area this has been attributed to fluctuation in the size and virulence of the avian mammalian vector pool[21,31] in its contact with and transmission of the agents to man and in the nature of human disease produced[32,33] Although chlamydial agents are widespread throughout the world there have been few studies specifically designed

*Note: This is not to be confused with statistical p values measuring significance. This P value is defined as the per cent of meningopneumonitis particles labeled with P^{32} precipitated by test serum.

Table VI. Results of additional serologic tests performed on selected sera of 16 PMD patients displaying complement fixing antibody to chlamydial agent (psittacosis human diagnostic antigen)

Test done	IBM patient identification No.																No. of sera tested
	1	10	14	17	24	30	31	34	44	59	69	72	76	80	110	121	
	Clinical diagnosis*																
	V	ASHD	AL	AL	V	V	V	PP	PP	V	V	V	V	AL	RHD	V	
1. Radioisotope precipitation (RIP) test corrected P value range†					65 64 62 0	32 32 32 30 25 25 25 25		30 38 25 30		63 63 63 63 63 63 64 58	70 67 65 63 65 65 63	70 63 62 62	60 55 53 53 50 50 45 40	73 70 70	57 57 57		49
2. Maximum titer to chlamydial agent in 3 or more sequential sera, tested simultaneously	32	4		32	128		256		128	128						64	30
3. Maximum titer to chlamydial agent, serial testing, serum control‡	16	32	32	32	256	64	128	256	16	128	64	128	256	256	64	32	183

*V Acute or chronic viral pericardium-myocardium; AL, alcoholic cardiomyopathy; PP, postpartum cardiomyopathy; RHD, rheumatic heart disease; ASHD, arteriosclerotic heart disease with cardiac infarction.
†RIP test: Corrected P value—per cent macromolecular particles labeled with P[32] precipitated by test serum (normal, −30 to +20). Performed by Dr. R. Gerloff, Rocky Mountain Laboratory, United States Public Health Service.
‡Maximum CF titer to chlamydial agent in sequential sera tested individually and compared to serum control. In the individual patient the number of sera available varied from 4 to 23.

to define their role in development of cardiac disease. For these reasons, the relationships which appear plausible between chlamydial infection and subsequent perimyocardial disease and which have arisen from long term surveillance in Illinois may not be applicable to other geographical areas. Long term serologic follow-up of patients with PMD has not been done elsewhere.[36] Only through long term sequential resampling and measurement of CF antibody titer in patients with PMD did data emerge which suggested an association between chlamydial infection and this form of heart disease.

Although the fluctuation in the number of PMD patients showing CF antibody titer to chlamydia was temporally and directionally synchronous with the increased incidence of such reactions in the noncardiac patients tested, the percentage of PMD patients showing this response to chlamydial agents was far greater than in the control population or in patients with cardiac disease of known etiology. Further there appears to have been a rise in the total number of newly detected patients with PMD during the same period. These findings are open to several interpretations.

(1) They could represent an absolute increase in the number of new patients in whom PMD was caused by chlamydial agent. Our data suggest that at least 20 patients in the study group first developed PMD during the course of this chlamydial outbreak.

(2) In the 14 patients who showed no worsening of their heart disease but a rise in titer it could be a reactivation of the serologic response to previous chlamydial infection (an anamnestic reaction).

(3) In six other patients who showed one

Table VII Comparative epidemiological data from State of Illinois Viral Laboratories and Cook County Hospital for years 1961 1967 Number of patients with and without PMD with sera reacting to chlamydial antigen*

Year	Data from State of Illinois			Data from Cook County Hospital		
	No of sera examined for chlamydial antibody	Positive sera detected		No of new PMD patients	Patients with PMD and sera positive for chlamydial CF antibody	
		No of noncardiac patients	Positive sera as per cent of total examined		No. of patients	Per cent of total
1961	1 591	46	2 9	28	1	4
1962†	3 230	35	3 3	27	4	15
1963†		72		76	19	25
1964	1 894	32	1 6	60	12	20
1965	2 592	49	1 9	30	12	20
1966	1 806	7	0 4	41	2	5
1967	1 627	6	0 4	57	0	0
Total	12 743	245	1 9	319	40	13

*Significant complement-fixing titers to psittacosis human diagnostic antigen, Markham Laboratories, Chicago, Ill., multiple titers of 1:32 or higher or fourfold decline, or single titers of 1:64 or lower

†Change in date of fiscal year of reporting.

or more recrudescences of their heart disease and associated serologic response it could be explained as a reactivation of a quiescent inflammatory perimyocarditis which had been initiated in the past by previous chlamydial infection

(4) Or finally these observations could merely be a reflection of a chlamydial epidemic affecting the general population as well as patients with PMD This latter possibility seems unlikely since patients of similar age with other forms of heart disease such as that due to rheumatic fever who were followed during this same period failed to show such a response to chlamydia This suggests that there was something distinctive about the response of the PMD patients in the face of this outbreak As previously noted PMD patients showed a much higher incidence than did any other group

The clinical manifestations of heart disease in PMD patients were similar regardless of their serologic status i e. whether or not they had antibody to Chlamydia. This indicates either that the role of Chlamydia in the production of PMD is not *clinically* evident or that the development or presence of PMD masked any *clinical* features of viral infection The failure to consistently identify a psittacine avian vector deserves note The avian vectors which were reported included four species of birds, among these *Turdus migratorius* (the common robin)

Although none of the stool cultures obtained from nine dead parakeets brought in by afflicted patients were positive for psittacosis agent wide distribution of chlamydial agent has been recognized among Chicago pigeons and other Illinois birds and mammals.[18] The latter includes dogs and human beings

The failure in this study to identify a particular vector in the majority of cases may be traceable to the existence of nonrecognized modes of transmission For example the chlamydial agent of trachoma has been cultured from the genitourinary tract of patients and their sexual partners.[19] The venereal route of transmission may have been operative in cases of postpartum PMD the dissemination of chlamydial agent from the genital tract during delivery appears plausible

Other forms of intercurrent cardiac dis-

ease were common in PMD patients. Since the origins of noncobaltous PMD associated with alcoholism and of postpartum PMD remain obscure, the serologic evidence of chlamydial infection in our study population is of particular interest. Our data suggest that this is not coincidental. Alcoholism pregnancy or other factors may set the stage for subsequent viral infection and damage of the heart.[17] This concept, however is difficult to prove.

The occasional occurrence of chlamydial infection of the myocardium superimposed on existing cardiac diseases of known etiology such as arteriosclerosis of the coronary arteries and rheumatic valvular disease, seems epidemiologically inevitable. The diagnosis of two concurrent cardiac diseases of diverse etiology should be more commonly considered. Burch and co-workers[19] have demonstrated fluorescent antibody to Coxsackie virus in the myocardium of 24 per cent of hearts of children dying of diverse causes. Further Nicolau and associates[20] have been able to culture pararickettsia agents from the blood of patients with arteriosclerotic coronary artery disease. In many instances, the evaluation of the relative contribution of each disease to over all cardiac dysfunction is not really possible.

Finally misdiagnoses may contribute to the relatively low reported incidence of heart disease of chlamydial origin. Pruitt and associates[21] first called attention to the production of electrocardiographic changes of dead myocard um or infarct in PMD Such infarct patterns in ECG or VCG were seen in both our chlamydial and non chlamydial groups of PMD patients and falsely suggested the presence of coronary disease. Only part of our study population had their coronary arteries examined by angiography visual inspection, manual palpation or postmortem assessment. With one exception, there was no significant evidence of coronary disease found. In those patients in whom myocardial biopsy or postmortem tissue was obtained, myocardial tissue diagnosis did *not* reveal infarcts. The histological character of the myocardial tissue obtained was that of hypertrophy and interstitial fibrosis or normal tissue. Myocarditis based on round cell infiltration was seen in four cases but was not of a specific type. Thus, our experience confirms the observations that myocardial fibrosis of noncoronary origin may produce ECG and VCG changes of infarct.

The complement fixing antibody present in the 40 PMD patients was felt to be specific for Chlamydia for the following reasons

(1) *Serial* testing of patient sera with three different egg-grown Chlamydia antigens revealed CF antibody persisting over a period of months to years. Hence, variability in production and harvesting of the test antigen did not influence these findings.

(2) *Simultaneous* testing of stored sera was done in two fashions (CF and RIP) and both methods confirmed the presence of antibody which reacted only to Chlamydia agent. In the course of these studies, it was demonstrated among the sera of these PMD patients that there was no cross reactivity to uninfected egg tissue or to other viral antigens. Stored sera of these patients was checked simultaneously for chlamydial antibody using P^{32}-labeled meningoencephalitis agent grown on mouse fibroblasts. Every sera except one reacted very strongly under this test system also.

(3) The sera of the PMD patients did not react with virus-altered host tissue, i.e., chicken egg allantoic membrane in which Newcastle disease virus was grown. It was considered possible that the CF antibody described in the patients was reacting to some altered portion of the chicken egg or to some product of virus in egg

(4) The sera of PMD patients who were reacting to Chlamydia did not react to Coxsackie antigen, nor did the sera of patients reacting to Coxsackie virus react to Chlamydia antigen. Hence, the most commonly recognized cause of inflammatory PMD the Coxsackie virus, could not be incriminated in these patients.

(5) The duration of the serologic reactivity to Chlamydia in these patients was very protracted. About half of the patients continued to manifest CF antibody to Chlamydia over the entire period of observation, running from one to more than five years. Such persistence of serologic reactivity has been well described by Strauss[22] in chlamydial respiratory disease.[23]

Tissue from 12 hearts was available for light microscopic study Although the large noninfectious form of Chlamydia in the host cell is 1μ in diameter in no case was any chlamydial agent seen nor was there any histologic alteration specific for viral invasion all tissues were either normal or consistent with PMD

Summary

Northern Illinois experienced an out break of chlamydial infection in 1963 1964 and 1965 as reflected by an increase in the number of patients showing antibody to this group of agents during the period Among these individuals, a disproportion ately large number with PMD showed serologic activity against Chlamydia This suggests that there was something distinc tive about the response of the PMD patients in the face of this outbreak.

The clinical manifestations of heart disease in PMD patients were similar regard less of their serologic status i e whether or not they had antibody of Chlamydia. Specific serum reactivity to Chlamydia was verified by (1) use of multiple chlamydial antigens (2) application of both complement fixation and RIP test systems, and (3) absence of reactivity to uninfected egg tissue or to egg tissue infected with New castle disease virus. Reactivity to Chla mydia persisted in our PMD population for periods of months to more than five years While the evidence cited in this paper linking chlamydial agent to the PMD is inferential and no direct evidence of chla mydial infection was found in the tissue of 12 hearts examined epidemiologic consid erations strongly suggest an etiologic rela tionship

REFERENCES

1 Schiraldi, O and Pisce, M Pleuro-pericardite in Soggetti con positivita della reazioni di deviazione del complemento per l ornitosi-psittacosi Policlinico Prat. 72 1603 1965
2. Schoenemann J von, and Glasel, E Akute benigne Perikarditis bei Ornithose, Z Ges. Inn. Med. 20:121 1965
3 Tesărová J Grantová H. and Milek, E. Kardio vaskulární Změny u nemocnych Orni tozou Cas. Lek. Cesk. 105:985 1966.
4. Stephan, E. Nachabe, Y Khoury M and Issa B Pericardites de la psittacose. A propos de 3 cas, Arch. Mal. Coeur 59 1257 1966.
5. Coll, R. and Horner I Cardiac involvement in psittacosis, Brit. Med. J 4:35, 1967
6. Schaffner W Drutz, D J., Duncan, G. W and Koenig M G. The clinical spectrum of endemic psittacosis, Arch. Intern. Med. 119:433, 1967
7 MacLennan, W J and Dymock, I. W Cardiac involvement in psittacosis, Brit. Med. J 1:620 1967
8. Valasek, W: Erfahrungen mit Ornithose erkrankungen bei der Wiener Bevolkerung, Wien. klin. Wschr 11:810 1967
9 Sutton G. C., Morrissey R. A., Tobin, J R, and Anderson, T O: Pericardial and myocardial disease associated with serologic evidence of infection by agents of the psittacosis-lymphogranuloma venereum group (Chlamydiaceae) Circulation 26:830, 1967
10. Adamy G. Klinische Studie uber die Psittakose, Deutsch. Arc. Klin. Med. 169:301, 1930
11 World Health Statistics Annual 1964, vol. II, p. 132 Publ. W H O Geneva 1968.
12. Steele, J H and Scruggs, J H. The epidemiology of psittacosis 1951 1956, in Beaudette, F R. editor Progress in psittacosis research and control New Brunswick, N J 1958, Rutgers University Press, pp. 32 51
13 Meyers, K. F and Eddie, B. A review of psittacosis for the years 1948-1950, Bull. Hyg 26:1 1951
14 Annual Summary Psittacosis 1968, National Communicable Disease Center zoonoses surveillance U S. Dept. H.E.W., Table I March, 1969
15 Tobin J R. Jr Driscoll J F Lim, M. T Sutton G. C. Szanto, P B and Gunnar R. M Primary myocardial disease and alcoholism, Circulation 33:754 1967
16. Friedberg C. K. editor Primary myocardial diseases and the myocardiopathies, I Progr. Cardiovasc. Dis. VII: July 1964
17 Hugenholtz, P G. Whipple, C H. and Levine, H D A clinical appraisal of the vectorcardiogram in myocardial infarction. I. The cube system, Circulation 24:808, 1961
18. Gerloff R. K. and Watson, R. O Radioisotope precipitin test for psittacosis group antibody Bact. Proc. No. 121 1966.
19 Sutton, G C. Driscoll J F Gunnar R. M., and Tobin, J R. Jr Exploratory mediastinotomy in primary myocardial disease, Progr Cardiovasc. Dis. 7:83 1964
20. Gerloff R. K. and Watso R. O The radioisotope precipitation test for psittacosis group antibody Amer J Ophthal. 63:1942 1967
21 Gordon, I: The diagnosis of human infection, in Beaudette, F R. editor Progress in psittacosis research and control New Brunswick, N J 1958, Rutgers University Press.
22. Strauss, J Microbiologic and epidemiologic aspects of duck ornithosis in Czechoslovakia, Amer J Ophthal. 63:1246, 1967
23 Gard S. Respiratory virus infections other than influenza Arch. Environ. Health 17:543 1968.

24. Fletcher G. F Coleman, M T Feorino, P M Marine, W H., and Wegner N K. Viral antibodies in patients with primary myocardial disease, Amer J Cardiol. 21:6, 1968.
25. Shaughnessy H. J Psittacosis in wild pigeons, in Beaudette, F R editor: Psittacosis, diagnosis, epidemiology and control New Brunswick, N J 1955 Rutgers University Press, pp. 90-98.
26. Da son, C. R., and Schachter J TRIC agent infections of the ey and genital tract, Amer J Ophthal. 63 1288, 1967
27 Shaper A. G. Myocarditis and cardiomyopathy East African Med. J 45:584 1968 (editorial)
28. Castleman, B., and McNeely B. U Weekly clinicopathological exercises—case 43—1966, New Eng J Med. 275:835, 1966.
29 Burch, G. E., Sun, S. C., Chu, K. C., Sohal, R. S., and Colcolough, H. L Interstitial and Coxsackie virus B myocarditis in infants and children, J.A.M.A. 203:1, 1968.
30. Nicolau, S. S., Sorodan, C. Sărăteanu, D Athanasiu, P and Anagnoste, B. Isolement de virus d sang d quelques malades atteints d affections cardio-vasculaires, Rev Sci. Med. (Bucur) 6 181 1961.
31 Pruitt, R. D., Curd, G. W Jr and Leachman, R.. Simulation of electrocardiogram of apicolateral myocardial infarction by myocardial destructive lesions of obscure etiology (myocardiopathy), Circulation 25:506, 1962.
32. Sery V Strauss, J Fastova-Mazel, J., and Voodrack, V Immunological survey of ornithosis in the population of the Czech regions, J Hyg. Epidem. (Praha) 5:439 1961.

Computer analysis of the orthogonal electrocardiogram and vectorcardiogram in 1,002 patients with myocardial infarction

E. E. Eddleman, Jr., M.D.
Hubert V. Pipberger, M.D.
Washington, D. C.

The electrocardiogram (ECG) remains one of the most clinically useful tools in the diagnosis of myocardial infarction (MI). It is well known, however, that a certain number of infarct cases can be missed on routine ECG and tracings may either remain within normal limits or show only nonspecific changes (false negatives). On the other hand, ECG findings characteristic for myocardial infarction may be found in a few normal subjects or in patients without evidence of myocardial infarction at autopsy (false positives).

Since the advent of corrected orthogonal lead systems, many reports have appeared in the literature[1-21] either advocating new diagnostic criteria for myocardial infarction or retesting those already proposed. Most reports claim the diagnostic superiority of orthogonal leads as compared to conventional 12 lead ECG's. In two autopsy studies,[13,14] however, this superiority in part was offset by a substantial increase in false positives, i.e., the gain in sensitivity might have been due in part to a concomitant loss in specificity. When Simonson and co-workers[22] compared interpretations of 12 lead records with those of vectorcardiograms (VCG) in a series containing many MI cases, only a small difference in diagnostic accuracy was noted but the results were definitely in favor of the conventional ECG.

Therefore, it appeared indicated to re-evaluate the performance of the orthogonal ECG and VCG for the diagnosis of MI on the basis of large, well-controlled samples of MI cases together with normal controls from subjects of the same age group. Records were analyzed by digital computer. Such methods provide several unique features. Complex mathematical procedures can be performed, such as discriminant function analysis, which are not feasible by routine methods. In addition, statistical techniques can be used which allow selection of optimal diagnostic ECG measurements to be used in routine record analysis. Large numbers of diagnostic criteria can be evaluated side by side for

From the Veterans Administration Cooperative Study on Automatic Cardiovascular Data Processing, Veterans Administration Hospitals, Birmingham, Ala., Dallas, Texas, Durham, N. C., Houston, Texas, Minneapolis, Minn., San Francisco, Calif., Washington, D. C., and West Roxbury, Mass., and the Departments of Medicine, University of Alabama School of Medicine, Birmingham, Ala., and Georgetown University School of Medicine, Washington, D. C.

Supported in part by Research Grants HE 09696 and HE 11310 from the National Heart and Lung Institute, United States Public Health Service.

Received for publication July 2, 1970.

Reprint requests to: Hubert V. Pipberger, M.D., Veterans Administration Hospital, Washington, D. C. 20422.

their efficiency The present study represents a comprehensive computer analysis of orthogonal ECG s from 1,002 patients with proved myocardial infarction.

Material and methods

Patient selection Records included in this study were obtained through a cooperative study of eight V A. hospitals. All patients had a clinically documented myocardial infarct. The most pertinent data of each case were recorded on uniform study protocols. Criteria for diagnosis of acute myocardial infarction included a typical history of a prolonged episode of substernal, crushing chest pain. In addition, records were available at that time or in previous hospital admissions to document the typical hospital course of the patient with a myocardial infarction and all patients had elevated enzyme studies during the course of the hospitalization The ECG was deliberately not used as a criterion for a myocardial infarction in the selection of patients since this would automatically bias the results of this study The only electrocardiographic consideration given was to exclude patients with ventricular conduction defects (QRS duration of 0.126 second or more) Records were taken during the acute phase of the infarction (first 6 weeks) in 392 (39 per cent) patients and later in 610 (61 per cent) patients. The normal subjects used for comparison gave no histories compatible with a myocardial infarction Again electrocardiographic criteria for abnormality were deliberately not considered as to whether these patients were normal or abnormal.

Data acquisition and processing Orthogonal ECG s were recorded on magnetic tape, with the use of the Frank[18] system with the chest electrodes at the level of the fourth intercostal space as recommended for the supine position.[18] A routine 12 lead ECG was also taken on all patients. Careful attention was given to the proper organization of the cooperative study in order to assure uniform recording techniques and standardized equipment performance and maintenance.

Details of analog to-digital data conversion and computer analysis have been reported previously [18] A Control Data Corporation 3200 digital computer was available for the study A total of 333 different scalar and vector measurements[14] were computed for each record in order to search for optimal discriminators between tracings from patients with MI and the normal control subjects. The latter consisted of 229 records from normal subjects of 40 years and older [17]

Data analysis To answer the question "MI or no MI the *total* of 1 002 MI records was tested first. Subsequently a subdivision of the MI sample was achieved on the basis of *QRS morphology* *Loss of* initial forces in the anterior direction was equated with anteroseptal or anterior MI (heretofore labelled anterior MI" group) This finding is expressed electrocardiographically as loss of *Q in Lead Z* (corresponding to loss of R in the first precordial leads) or an abnormally low Q/R amplitude ratio of less than 0 10

The Q/R_Y ratio was used for initial grouping of cases with posterodiaphragmatic MI Records exceeding the normal limit of 0.22 were included in this group (corresponding to Q-wave abnormalities in Leads II III and aV_F) For classification of lateral MI cases the normal limit of 0.21 of the Q/R_x ratio was used (corresponding roughly to Q abnormalities in Leads I aV_L, V_5, or V_6)

Out of the total of 1,002 records, 268 fell into the anterior MI group (AMI) 317 into the postero-diaphragmatic MI group (PDMI) and 111 into the lateral MI group (LMI) These were considered as core samples with 306 records remaining unclassified. In order to classify the records of the latter group, a computer program for diagnostic classification was used which is based on discriminant-function analysis and a likelihood ratio test.[14] Eight instantaneous QRS vectors were used as variables. Distances between each unclassified record and the three core groups were determined and the tracing was assigned to the group which was closest to it. In essence, this procedure tests *similarity* in QRS configuration. Thus, each record from patients with the clinical diagnosis of myocardial infarct could be assigned to one of the groups 377 to AMI 512 to PDMI and 113 to LMI Q/R amplitude *ratios*

were used for formation of the core groups because this criterion was found to exceed all others in the identification of MI records [14]

It has to be kept in mind however that the classification into subgroups with a connotation of infarct location is based strictly on QRS morphology A correlation between these groupings and anatomic findings in 240 autopsy cases will be reported elsewhere.[15]

Computer classification Initially the rec ords were screened for 333 different vari ables[16] in order to identify the best discriminators. Since most ECG variables are not normally distributed 96 percentile ranges of normal were used first and the number of cases which exceed the limits of these normal ranges was determined The 30 best measurements were then subjected to linear discriminant function analysis. A discussion of this technique has been ade quately presented previously [11] Neverthe less it should be mentioned that the procedure represents a mathematical method of separating groups of data and selecting variables which are most efficient for this end Discriminant function coefficients which are computed for each variable indicate their relative importance for the discrimination or their weight factors. Each ECG measurement is multiplied with its corresponding coefficient and the products of all measurements used are added to form a patient vector which needs to be classified Thus this patient vector contains information of a multi tude of variables which are all properly weighted according to their respective con tributions to differentiation between groups Since certain variables are of smaller magnitude than others (e g S-T ampli tudes) the product with a large coefficient may still result in a relatively small con tribution whereas, a larger variable (e g R amplitudes) with a smaller coefficient can still be more important. Therefore the data are presented in two ways—the initial coefficients normalized to one and the products of the coefficients with the means of the variables

Empirically it has been found that the number of discriminators used in multi variate analysis should not exceed the

*Table I ECG measurements found best for the differentiation between normal and the total series of 1,002 MI cases regardless of MI location**

	Variable	Discriminant	Product†
1	3/8 QRS_{XY}	0 55	496
2	Spatial maximum QRS	0 31	439
3	Maximum QRS_{XZ}	−0 33	402
4	3/8 QRS_{XZ}	−0 38	344
5	2/8 QRS_{XY}	−0 83	252
6.	R_Z	0 25	201
7	2/8 QRS_{XZ}	0 48	190
8.	R_Y	0 20	139
9	T	0 90	100
10	T_Y	1 00	94
11	Q	0 74	62
12	5/8 QRS_Y	−0 24	45
13	1/8 QRS_Z	−0 46	43
14	S	0 41	42
15	2/8 QRS_Z	−0 21	29

*The selection of variables was based on linear discriminant-function analysis. The coefficients in the second column represent weight factor and each measurement needs to be multiplied by this factor The true contribution to differentiation is indicated by the product of the coefficients and the averaged means of the normal and abnormal groups (multiplied by 1 000) and shown in the last column. Note the minor contributions of the last variables. Measurements labelled 1/8, 2/8, and so on, are amplitudes derived from time-normalized QRS or ST T complexes, obtained by dividing these complexes in time into 8 equal parts.

†Products of mean measurements and discriminant-function coefficients (multiplied by 1 000)

square root of the smallest sample under study because too many variables may lead to overoptimistic results which cannot be repeated on new and independent sam ples Each set of variables was, therefore reduced from 30 to this number selecting the highest discriminant function coeffi cients and taking into consideration the sample size A likelihood ratio test was then used for classification of individual records.[11]

The hierarchy of best discriminators ob tained from 96 percentile ranges of normal served also as basis for determination of optimal ECG measurements which can be recommended for routine use Only vari ables which can be easily measured from scalar leads or planar VCG displays were selected Great care was taken to eliminate redundant information and to reduce the percentage of false positives to a minimum

Table II Classification of patients according to MI location

	With discriminant function analysis on orthogonal leads		*Classification of 12 lead ECG according to Minnesota Code I 1**	
	Correctly classified (%)	*Misclassified (%)*	*Correctly classified (%)*	*Misclassified (%)*
Total MI series (1,002 patients)				
MI	84	16	49	51
Normals	94	6	94†	6†
Anterior infarctions (377 patients)				
AMI	86	14	38	62
Normals	95	5		
Postero-diaphragmatic infarctions (512 patients)				
PDMI	88	12	53	47
Normals	95	5		
Lateral infarctions (113 patients)				
LMI	98	2	66	34
Normals	100	0		

*Classification results of the total MI series and the three subgroups, AMI, PDMI, and LMI. Note that the classifications of the subgroups are slightly more efficient because of the more homogeneous record samples. Classification on the basis of conventional 12 lead electrocardiograms, shown in the last two columns, is based on Code I.1 of the Minnesota Code in order to maintain comparable level of specificity for the two methods (5 to 6 per cent false positives).
†The classification rates of the 12 lead ECG for normals are based on 615 autopsy cases of subjects with normal hearts, reported by Kaplan and associates.

with the use of methods described previously.[20]

In order to test the repeatability of results, computations were performed first on 466 records from patients with MI and repeated later on the remaining 536 MI case records. An additional independent sample consisted of records from 240 cases exhibiting at autopsy myocardial infarcts of at least 2 cm in one dimension.

To compare computer classifications with 12 lead ECG analysis, findings of each conventional ECG were coded according to the Minnesota Code.[21]

Results

Separation of total infarction group from normal. Discriminant function analysis was performed initially on the total MI sample of 1,002 records and the normal control of 229 tracings. A total of 15 variables was selected which are listed in Table I together with the discriminant-function coefficients. With the use of this technique 84 per cent of the MI cases and 94 per cent of the normal subjects were properly classified (Table II). Consequently, 16 per cent of the MI patients were classified as normal (false negatives) and 6 per cent of normal subjects were erroneously placed in the MI group (false positives).

Separation of each infarction group from normal. The total series of records from patients with myocardial infarcts was subdivided according to general infarct location on the basis of QRS morphology as described under Methods. Each subgroup was then tested against the normal control group. Table II presents the findings. Note that there was a slight-to-moderate increase in sensitivity when more homogeneous samples according to infarct location were used. The false positive rate was kept at 5 per cent or below, thus maintaining a constant specificity. Poorest results were obtained with 86 per cent for AMI and best results were obtained for LMI with 98 per cent, with PDMI being in between.

Tables III, IV, and V list the discriminant function coefficients used for these classifications. Note that vector measurements exceed the scalar variables substantially in their contribution to differentiation.

Fig. 1 gives a breakdown of the 84 per

were used for formation of the core groups because this criterion was found to exceed all others in the identification of MI records.[14]

It has to be kept in mind however that the classification into subgroups with a connotation of infarct location is based strictly on QRS morphology. A correlation between these groupings and anatomic findings in 240 autopsy cases will be reported elsewhere.[19]

Computer classification. Initially the records were screened for 333 different variables[14] in order to identify the best discriminators. Since most ECG variables are not normally distributed 96 percentile ranges of normal were used first and the number of cases which exceed the limits of these normal ranges was determined. The 30 best measurements were then subjected to linear discriminant function analysis. A discussion of this technique has been adequately presented previously.[11] Nevertheless it should be mentioned that the procedure represents a mathematical method of separating groups of data and selecting variables which are most efficient for this end. Discriminant function coefficients which are computed for each variable indicate their relative importance for the discrimination or their weight factors. Each ECG measurement is multiplied with its corresponding coefficient and the products of all measurements used are added to form a patient vector which needs to be classified. Thus this patient vector contains information of a multitude of variables which are all properly weighted according to their respective contributions to differentiation between groups. Since certain variables are of smaller magnitude than others (e.g. S-T amplitudes) the product with a large coefficient may still result in a relatively small contribution whereas a larger variable (e.g. R amplitudes) with a smaller coefficient can still be more important. Therefore the data are presented in two ways—the initial coefficients normalized to one and the products of the coefficients with the means of the variables.

Empirically it has been found that the number of discriminators used in multivariate analysis should not exceed the square root of the smallest sample under study because too many variables may lead to overoptimistic results which cannot be repeated on new and independent samples. Each set of variables was, therefore, reduced from 30 to this number selecting the highest discriminant function coefficients and taking into consideration the sample size. A likelihood ratio test was then used for classification of individual records.[18]

The hierarchy of best discriminators obtained from 96 percentile ranges of normal served also as basis for determination of optimal ECG measurements which can be recommended for routine use. Only variables which can be easily measured from scalar leads or planar VCG displays were selected. Great care was taken to eliminate redundant information and to reduce the percentage of false positives to a minimum

*Table I. ECG measurements found best for the differentiation between normal and the total series of 1 002 MI cases regardless of MI location**

	Variable	Discriminant	Product†
1	3/8 QRS_{XY}	0 55	496
2	Spatial maximum QRS	0 31	439
3	Maximum QRS_{XZ}	−0 33	402
4	3/8 QRS_{XZ}	−0 38	344
5	2/8 QRS_{XY}	−0 83	252
6.	R_{Z}	0 25	201
7	2/8 QRS_{XZ}	0 48	190
8	R	0 20	139
9	T	0 90	100
10.	T	1 00	94
11	Q	0 74	62
12.	5/8 QRS_{Y}	−0 24	45
13	1/8 QRS_{Z}	−0 46	43
14	S_{Y}	0 41	42
15	2/8 QRS_{Z}	−0 21	29

*The selection of variables was based on linear discriminant-function analysis. The coefficients in the second column represent weight factors and each measurement needs to be multiplied by this factor. The true contribution to differentiation is indicated by the product of the coefficients and the averaged means of the normal and abnormal groups (multiplied by 1 000) and shown in the last column. Note the minor contributions of the last variables. Measurements labelled 1/8, 2/8 and so on, are amplitudes derived from time-normalized QRS or ST T complexes, obtained by dividing these complexes in time into 8 equal parts.

†Products of mean measurements and discriminant-function coefficients (multiplied by 1,000).

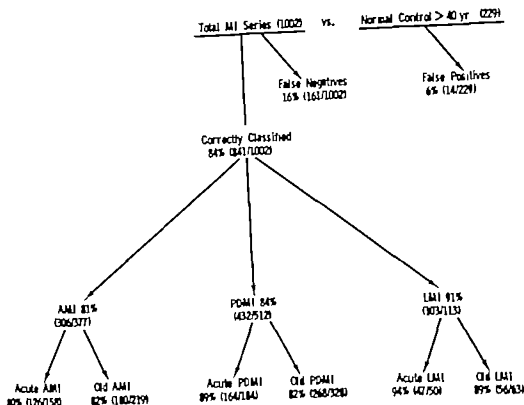


Fig. 1. Differentiation between the total MI series and normal. The further breakdown indicates classification according to MI location, based on QRS morphology.

tients with MI according to the Minnesota Code.[22] In order to make the orthogonal and 12 lead data comparable, only Code 1 1 was used (Table II) which according to the comprehensive autopsy study of Kurihara and co-workers[20] yields a false positive rate of only 6 per cent. Thus, the level of specificity was kept at a comparable level for orthogonal and conventional leads. The percentage of correct classifications for the latter varied between 38 and 66 per cent depending upon MI location. When codes 1,2 and 1,3 were used in addition to 1 1 the number of correct classifications increased substantially (Table VI) but the rate of false positives rose at the same time from 6 to 16 per cent.

Classification by methods which can be applied to standard recordings. As mentioned earlier one goal of the study was the identification of optimal discriminators which can be obtained with relative ease from orthogonal-scalar lead or planar VCG displays. Table VII lists the variables along with limits proposed for separation of normal and MI records with false positive rates.

Out of the AMI group 79 per cent could be classified correctly on the basis of only two QRS variables, the Q/R ratio and the R duration. To achieve a separation of normals versus PDMI of similar magnitude (77 per cent) four QRS measurements were necessary. Best results were achieved for LMI with 98 per cent but it should be kept in mind that 111 of the 113 cases of this group were selected on the basis of the Q/R ratio. Therefore, this sample remained more homogeneous than the others.

When T wave changes were used in addition to QRS variables the separation was improved up to 5 per cent, but such changes by themselves may of course, be nonspecific.

False positive rates were kept at 5 per cent or less for QRS measurements. The limits of the variables differ slightly from 96 percentile limits of normal. This was done to adjust false positive rates and in

*Table III ECG measurements which proved best for the differentiation between normal records and those from patients with anterior MI (377)**

	Variable	Discriminant	Product†
1	Maximum QRS_{XZ}	−0 37	468
2	Spatial maximum QRS	0 26	386
3	3/8 QRS_X	0 46	335
4	3/8 QRS_{XZ}	−0 21	195
5	2/8 QRS_{XZ}	0 44	173
6	2/8 QRS_X	−0 63	144
7	Q_Z	−0 61	130
8	T_X	1 00	88
9	3/8 QRS_Z	0 16	46
10	2/8 QRS_Y	−0 24	29
11	2/8 QRS_Z	−0 50	25
12	R_Z	0 01	9
13	1/8 QRS_Z	−0 08	6
14	Q_X	0 10	3

*For further detail see text and footnote to Table I.
†Product of mean measurements and discriminant-function coefficient (multiplied by 1,000)

cent (841/1 002) of MI cases which were correctly differentiated from normal Numbers with acute and old MI are indicated There was a surprisingly small difference between recognition rates of these two groups (86 per cent [337/392] for acute MI and 83 per cent [504/610] for old MI)

Mean patterns of scalar leads and vector cardiograms Figs. 2 3 and 4 present mean QRS and ST T complexes of the three MI groups together with the normal control These complexes were time normalized by dividing each one into eight parts and by computing a mean amplitude for each eighth Besides the characteristic Q-wave abnormalities which formed the basis for the grouping several other features seemed noteworthy In Fig 2 for instance the mean Lead Z configuration lacks all anterior forces and the question arises whether this group does not represent anterolateral infarcts rather than pure lateral lesions. Another striking feature particularly in the PDMI and LMI groups is the marked decrease of R waves in Leads Y and Y respectively following the expectedly large Q waves. Both these changes together explain the remarkable efficiency of Q/R amplitude ratios in the diagnosis of MI

*Table IV ECG measurements which proved best for the differentiation between normal records and those from patients with posterodiaphragmatic MI (512)**

	Variable	Discriminant	Product†
1	3/8 QRS_{XY}	0 80	744
2	3/8 QRS_X	−0 68	545
3	R_Y	0 29	191
4	R_Z	0 18	132
5	Q_Y	0 71	90
6	3/8 QRS_Y	−0 26	88
7	T_Y	1 00	75
8	4/8 QRS_Y	0 16	75
9	2/8 QRS_{XY}	−0 18	57
10	5/8 QRS_Y	−0 17	33
11	R_X	−0 03	31
12	S_Y	0 24	18
13	2/8 QRS_Y	0 85	11
14	3/8 ST T_Y	0 29	3

*For further detail, see text and footnote to Table I.
†Products of mean measurements and discriminant-function coefficients (multiplied by 1,000)

*Table V ECG measurements which proved best for the differentiation between normal records and those from patients with lateral MI (113)**

	Variable	Discriminant	Product†
1	Spatial maximum QRS	−0 33	448
2	Maximum QRS_{XY}	0 36	354
3	3/8 QRS_{XZ}	0 22	180
4	Q_X	1 00	148
5	Maximum QRS_{XZ}	0 12	138
6	T_X	0 80	58
7	R_X	−0 03	22
8	2/8 QRS_Z	−0 43	22
9	S_X	−0 07	9
10	4/8 ST T_Y	−0 24	6

*For further detail, see text and footnote to Table I.
†Products of mean measurements and discriminant-function coefficients (multiplied by 1,000).

It should be noted that most of the T changes seen in the MI groups correspond to those of patients with chronic infarcts. This is due to the larger number of subjects with old infarcts in the study

Classification according to the Minnesota Code Tables II and VI list the classification of conventional 12 lead ECG of the pa

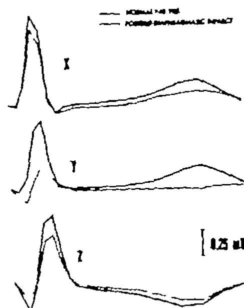


Fig. 3A. Mean scalar leads of 512 records from patients with postero-diaphragmatic MI. For method of averaging, see Fig. 2. Note the increase of the Q wave in Lead Y with a concomitant decrease of the R wave in this lead.

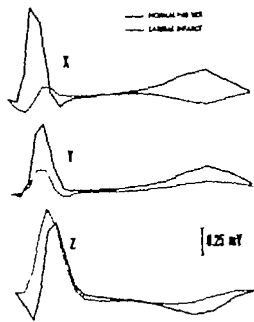


Fig. 4A. Mean scalar leads of 113 records from patients with lateral MI. For method of averaging, see Fig. 2. Note the increase of the Q wave in Lead X together with a marked decrease of Rx, indicating loss of lateral forces.

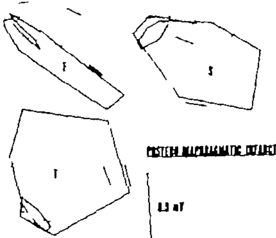


Fig. 3B. Vector loop projections of records shown in Fig. 3A.

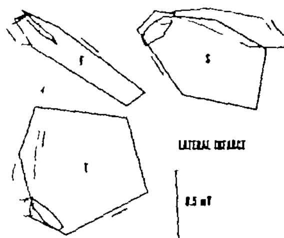


Fig. 4B. Vector loop projections of records shown in Fig. 4A.

by intolerably large rates of false positives which may exceed 30 per cent.

Part of the improvement in ECG differentiation of the present study can be attributed to the use of multivariate analysis and more specifically to discriminant function analysis. With this procedure, a series of carefully selected and properly weighted ECG measurements are used simultaneously for the separation of different diagnostic entities. Both the selection and weighting of variables are based on their discrimination power, i.e., the intrinsic goal of the computational process is the optimization of differentiation. In such applications, the full power of the digital

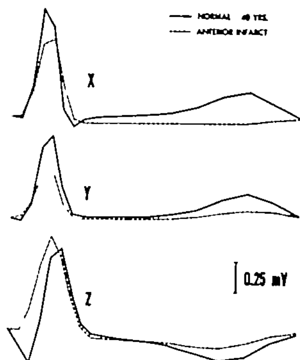


Fig. 2A Mean scalar lead of 377 records from patients with anterior MI and the normal control group The average configurations are based on time-normalized complexes where both QRS and ST T were divided in time into eight equal parts. Note the absence of Q in Lead Z of the AMI group, indicating loss of anteriorly directed forces

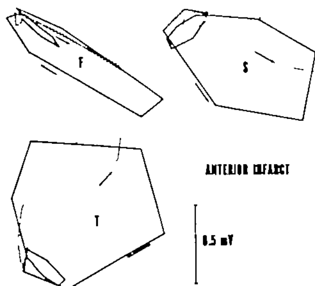


Fig. 2B Vector loop projections of records shown in Fig 2A

order to arrive at measurements which can be conveniently obtained from conventional paper-strip recordings.

Repeatability of results In previous studies it was found that in all classifications based on multivariate analysis it is mandatory to test initial results for repeatability with new and independent record samples. In general the use of many variables tends to lead to results which are better than those of repeat studies.

To circumvent these pitfalls, the described classification procedures were applied first to an initial sample of 466 records from patients with MI The record collection was continued until 536 more tracings had become available. Keeping the false positive rate constant at 6 per cent, 83 per cent (387/466) of the first sample could be separated from the normal[13] as compared to 85 per cent (454/536) for the second sample The closeness of the results seemed to indicate that both samples were probably large enough to be representative for the population under study and it was decided to merge them This led to the separation of 84 per cent of the total MI cases as shown in Table II and Fig 1

Repeatability of results was also tested with 240 records from patients who had had autopsies and had shown infarcts of at least 2 cm in one diameter[19] With the use of the same classification procedure and with the same variables and the same rate of false positives 88 per cent (210/240) could be classified correctly

Discussion

Reports on electrocardiographic recognition rates of myocardial infarcts in the literature vary widely and percentages between 20 and 75 have been reported depending on material studied and criteria used[1] Results obtained in the present study exceed these rates substantially With the use of independent samples, between 83 and 88 per cent of orthogonal ECG s from patients with myocardial infarcts could be differentiated from a normal control of the same age group The sample with the highest recognition rate of 88 per cent was derived from 240 autopsy proved MI cases[19] The false positive rate was carefully controlled not to exceed a maximum of 6 per cent. As shown by Gunnar and co-workers[15] and Murata and associates[16] who made detailed autopsy correlations, many efficient discriminators in common use may lead to high recognition rates for MI but this gain is largely offset

Table VII Measurements which can be made on routine orthogonal records

ECG measurements	*Limits used for separation and percentage outside these limits*	*Cumulative %**	*False positive (Cumulative %)*
Anterior infarctions:			
Q/R_z amplitude ratio	$<$ 0 10	71	3
R_z duration	$\leq$ 0 07 second	79	5
T amplitude†	$>$ 0 05 mV	83	7
Posterodiaphragmatic infarctions:			
Q/R_y amplitude ratio	$>$ 0 25	70	2
Q_y duration	$\leq$ 0 03 second	72	2
Q_y amplitude†	$<$ 0 24 mV	75	4
R peak time	$\geq$ 0 06 second	77	4
T amplitude†	$<-$0 10 mV	82	6
Lateral infarctions:			
Q/R_x amplitude ratio	$>$ 0 17	98	2
Total (3 MI groups)	Using all QRS criteria	80	8
	Using QRS and T criteria	84	12

*Including cases without Q.

†For negative values < means more negative and > means less negative or less positive.

when the *initial* question can be narrowed down to AMI versus normal or PDMI versus normal Such a situation may be encountered when ST or T changes point in a certain direction (e.g T inversion in Lead Y for PDMI) Only in such cases can the improved recognition rates of Table II be obtained. If all three MI locations and normal are considered simultaneously and the false positive rate is being maintained at 6 per cent, the over-all recognition rate will drop from 84 to 80 per cent. It is for this reason that MI as such should be differentiated from normal first, and the localization be considered only thereafter

A further problem is posed by differentiations against other ECG abnormalities. It is well known for instance that records from patients with pulmonary emphysema, with or without chronic cor pulmonale can mimic electrocardiograms of infarct patients, particularly those with AMI and PDMI Ishikawa and associates[11] have reported recently on efficient discriminators to separate MI from records of emphysema patients. The differential diagnosis of anterior MI and left ventricular hypertrophy poses another well-known problem particularly in cases without initial forces in anterior direction. Each of these problems requires an addition differentiation with a new set of discriminators.[12]

The applicability of linear discriminant function analysis to medical data has been questioned frequently because it is based on the assumption of normal data distribution which is frequently not found However Yasui and co-workers[14] investigated this problem and found that the use of multiple ECG measurements leads to multivariate normal distributions which would justify application of this technique. The highly satisfactory and repeatable results in other studies[12,13,18] lend further support to its applicability and usefulness.

It was interesting to note that out of the very large number of variables tested for multivariate analysis, vector measurements exceeded almost always scalar variables in their contribution to differentiation. Time coherence between leads appeared, therefore an important factor toward improvement in ECG classification which necessitates simultaneous recording of leads.

In the selection of measurements for routine ECG analysis, an earlier finding made by Naval and associates[16] on a smaller series of MI cases was confirmed. They found that Q/R amplitude ratios exceed all other diagnostic criteria in MI

*Table VI Classification of infarctions according to the Minnesota Code**

Code	No	%
Anterior myocardial infarctions (377 cases)		
1,1	143	38
1,2	79	21
1,3	19	5
Total	241	64
Posterodiaphragmatic infarctions (51 cases)		
1,1	271	53
1,2	113	22
1,3	10	2
Total	394	77
Lateral myocardial infarctions (113 cases)		
1,1	75	66
1,2	20	18
1,3	3	3
Total	98	87
Grand total (1,00 cases)		
1,1	489	49
1,2	212	21
1,3	32	3
Total	733	73
False positives† (615 cases)		
1,1	39	6
1,2	42	7
1,3	20	3
Total	101	16

*The ECG criteria of the Minnesota Code for the diagnosis of MI were designed in descending order, i.e., Code 1,1 contains the most rigid criteria and Code 1,3 the more liberal ones. Application of all three codes leads, therefore, to the highest recognition rates but they are partially offset by the increasing rate of false positives.

†Based on 615 autopsy cases without myocardial infarction according to Kurihara and associates.[34]

computer is used to great advantage because the sheer amount of computations necessary in this process precludes conventional calculation methods. Once diagnostic matrices have been computed on the basis of large samples, however, computer classification of each new case requires only a very small amount of computer time.

Similar considerations apply when optimal discriminators are to be determined for hand measurements in routine ECG analysis. In the present study this search required testing and comparing 333 ECG variables side by side on 1,471 ECG's. Such a task might have required several man-years without access to automated facilities. Once it is performed, however, and the repeatability of results has been demonstrated on independent samples, considerable confidence is provided for further applications.

It is well known that electrocardiographic signs of MI may decrease or disappear in the months or years after the acute episode. Burns-Cox[23] and Kurihara and associates,[34] who have reviewed this problem most recently, have quoted autopsy studies where less than 30 per cent of ECG records from MI patients had been correctly interpreted to diagnose the disease prior to death. The high recognition rate of 83 per cent for old infarcts in the present study as compared to 86 per cent for the acute cases appeared most satisfactory, particularly in the light of the recognition rate of 88 per cent for the autopsy control. When the number of false negatives were considered by themselves, however, the number of old MI cases which were missed was still about twice as large as that of acute cases (106 versus 55).

Main emphasis in the present report was placed on the differentiation between MI and normal. The first question which is generally asked is: MI or no MI. In this context no information is provided on MI localization. As shown in Table II considerably higher recognition rates can be achieved when groups such as anterior or lateral MI are differentiated against the normal group. This procedure might be misleading, however, because each differentiation from normal has its own false-positive rate based on the specific measurements used (Tables III-V). A more realistic procedure is to differentiate first between MI (all localization) and normal and subsequently between the three groups AMI, PDMI, and LMI. Since the latter procedure was used for the initial grouping of all MI cases (see under Methods), it was not repeated later. With the methods used each case has to fall into one of these three categories since the choice is limited to three only.

A somewhat different situation exists

on orthogonal records. The results are more difficult to compare because of different levels of specificity. Allowing for 13 per cent false positives for the conventional ECG and for 8 per cent for orthogonal leads, the difference in correct MI classification *is only 10 per cent.* When both rates of false positives are adjusted to the same level, a difference of approximately 15 per cent has to be expected.

There are probably a multitude of factors which have contributed to this substantial improvement in ECG diagnosis of myocardial infarctions. As found in previous studies, multivariate analysis represents a distinct advantage in record classification. The simultaneous use of a series of weighted and optimized discriminators in multidimensional space may represent one of the most useful and practical contributions to ECG diagnosis made by computers. Identification of optimal discriminators for routine use also provides better information on relationships between various ECG measurements through more precise evaluation of the relationship between sensitivity and specificity. As pointed out earlier, truly reliable and repeatable results on large-scale evaluations of the diagnostic performance of ECG measurements require an enormous amount of computations on large record samples. These studies also point out the limitations of the ECG which are so easily underestimated. It has to be realized that even with the use of multivariate analysis, the the ECG diagnosis of MI will be missed in approximately one of six cases. At the same time, one of seventeen records from normal subjects will be erroneously classified as MI. Although these results represent a considerable improvement in ECG diagnosis, the limitations of the information content of the electrocardiogram have to be kept in mind. Nevertheless, it could be shown that computer technology and application of efficient statistical techniques can enhance presently available ECG classification methods.

Summary

Orthogonal ECG's (Frank system) were recorded from 1,002 patients with documented myocardial infarction. In 39 per cent of this series, tracings were obtained during the acute phase of the disease and in 61 per cent at a later date. Records from 229 normal subjects above the age of 40 years served as *control.* A total of 333 different ECG measurements were computed from each record in order to search for optimal discriminators between the group of normal subjects and the patients with myocardial *infarct.*

Using linear discriminant-function analysis with 15 different ECG variables, it was possible to identify correctly 84 per cent of the infarct series with 6 per cent false positives. When the total sample was subdivided on the basis of QRS morphology into anterior, postero-diaphragmatic, and lateral infarcts, the classification could be improved by 2 to 14 per cent. The results were tested on an independent record sample derived from 240 autopsy cases of myocardial infarcts. With the use of the multivariate classification procedure developed on the basis of the clinically diagnosed sample, 88 per cent of the autopsy cases could be diagnosed correctly.

Computer classification results were also compared with conventional 12 lead ECG interpretations with the use of the Minnesota Code. When the false positive rate was kept at 6 per cent for both methods, 49 per cent of the standard ECG's were classified correctly as compared to 84 per cent for orthogonal ECG's analyzed by computer.

In addition, optimal discriminators between normal and infarct records were determined for measurements which can be easily obtained by hand. Correct classifications decreased to 80 per cent with 8 per cent false positives. Q/R amplitude ratios proved most efficient.

Results of the study emphasize the need for efficient control of false positive rates because increases in diagnostic sensitivity are frequently offset by concomitant losses in specificity. Application of multivariate analysis techniques proved very efficient for diagnostic ECG classification by computer.

REFERENCES

1. Hugenholtz, P. G., Forkner, C. E., Jr., and Levine, H. D.: A clinical appraisal of the vectorcardiogram in myocardial infarction. II.

recognition This measurement combines information on Q and R abnormalities (Figs. 3 and 4) in one numerical term Further improvement in MI differentiation proved most difficult because the small gains made through additional measurements were usually completely offset by the concomitant increase in false positives. Since in each case where MI is suspected measurements for all MI locations need to be tested the combined false positive rate of 8 per cent is the most realistic figure Comparing these results with those obtained by multivariate analysis (Tables II and VII) a loss in sensitivity of 4 per cent and a loss in specificity of 2 per cent were found This leads to an over-all deterioration in classification by approximately 6 per cent. Or in other terms one may conclude from these data that multivariate analysis improved MI recognition by the same amount i e one MI case out of 17 would be missed if the set of optimal hand measurements were used instead of multivariate analysis.

The T wave criteria listed in Table VII could have been left out completely This is not only because they are by themselves not sufficiently specific to justify the diagnosis of MI but they were included only to illustrate an important point. Although it may appear that in each subgroup of MI the T wave contributed to the separation of MI versus normal the total percentages reveal that the gain of 4 per cent in MI recognition is completely offset by the increase of 4 per cent in false positives.

A further reason why one should always try to limit the number of diagnostic criteria is explained by the very nature of most medical data distributions. Whether they are normally distributed and the means and two standard deviations are used to define the limits of a range or whether 96 percentile distributions are used there will always be 2 to 3 per cent of the cases cut off on either end of the range. Such procedures have to be used in order to eliminate outlyers which should be excluded if the normal range is not to be unreasonably large. The use of 100 percentile ranges is unpractical for this reason These outlyers, however represent the real culprits which add to the false positive rates. Any increase in number of diagnostic criteria is therefore accompanied by a certain loss in specificity and it is only when the gain in sensitivity exceeds definitely this loss that additional criteria should be considered This phenomenon becomes already discernible when recognition rates and false positives for 4 QRS measurements are used in the diagnosis of PDMI (Table VII) or even more clearly when T parameters are included, as outlined earlier

Comparison of results between orthogonal and 12 lead ECG analysis always represents a problem because generally accepted diagnostic criteria are not available for the latter The Minnesota Code[11] is being used increasingly for correlation studies and contains probably the most widely used diagnostic criteria. Further more recognition rates for MI and false positive rates for this code have been reported based on the large autopsy correlations of Kurihara and associates.[23,24] Observer variability and difficulties in coding are definite shortcomings. The problems which are encountered in standardized application have been discussed by H Blackburn[37]

With the use of the Minnesota Code the MI recognition rates in the present study were 49 21 and 3 per cent for Code I 1 I 2 and I 3 respectively with a total of 73 per cent. These results were remarkably similar to those reported by Kurihara and co-workers[24] who obtained only slightly less in their autopsy study (total of 64 per cent) This comparison lends considerable confidence to the 12 lead analysis of the present series but it revealed at the same time a wide discrepancy between orthogonal and 12 lead results. In the most strict comparison with equal numbers of false positives (6 per cent) it was possible to identify 84 per cent of all MI cases as compared to 49 per cent with the conventional electrocardiogram a difference of 35 per cent. This difference is reduced to 11 per cent when one allows a false positive rate of up to 16 per cent for the conventional ECG (Table VI)

As could be expected the gain in diagnostic accuracy was considerably smaller when simple hand measurements were used

Matsushita, S., Seki, M., and Ikeda, M.: Reliability of abnormal Q and QS patterns classified by the Minnesota Code for the diagnosis of myocardial infarction in aged people, Jap. Heart J. 8:514, 1967.

33. Burns-Cox, C. J.: The occurrence of a normal electrocardiogram after myocardial infarction, Amer. Heart J. 75:572, 1968.

34. Kurihara, H., Kuramoto, K., Murata, K., Terasawa, F., Seki, M., and Ikeda, M.: Incidence of abnormal Q and QS patterns classified by the Minnesota Code in 74 autopsied cases of myocardial infarction in the aged, Jap. Heart J. 8:419, 1967.

35. Klein, P. M., Eddleman, E. E., Jr., and Pipberger, H. V.: Electrocardiographic differentiation between left ventricular hypertrophy and anteroseptal myocardial infarction, Circulation 42:875, 1970.

36. Yasui, S., Yokoi, M., Watanabe, Y., Mizuno, Y., and Hibino, S.: Computer diagnosis of electrocardiograms by means of the joint probability, Jap. Circ. J. 32:517, 1968.

37. Blackburn, H.: The electrocardiogram in cardiovascular epidemiology: Problems in standardized application, Ann. N. Y. Acad. Sci. 126:882, 1965.

The Frank system Circulation 21:825 1961
2. Pipberger H V and Carter T N Analysis of the normal and abnormal vectorcardiogram in its own reference frame, Circulation 25:827 1962
3. Pipberger H V Stallmann F W and Berson A. S. Automatic analysis of the P-QRS-T complex of the electrocardiogram by digital computer Ann. Intern. Med. 5 :776, 1962.
4. Walsh T J Tiongson I M Stoddard E A and Massie E.: The vectorcardiographic QRSsE loop findings in inferoposterior myocardial infarction, AMER HEART J 63:516 1962.
5. Libanoff A J Boiteau G M and Allenstein, B J Diaphragmatic myocardial infarction with peri-infarction block. Studies of the electrocardiogram and vectorcardiogram Amer J Cardiol. 12:772 1963
6. Abel H Der Herzinfarkt im orthogonalen Elektro- und Vektorkardiogramm Z. Kreislaufforsch. 5..:1057 1963
7. Hoffman I Taylor R. C Bootnick A. Vectorcardiographic residual of inferior infarction seventy-eight cases studied with the Frank system Circulation 29:562 1964
8. Yano, K. and Pipberger H V Spatial magnitude, orientation, and velocity of the normal and abnormal QRS complex, Circulation 29 107 1964.
9. Hoffman, I Taymor R. C Morris, M H and Kittell I Quantitative criteria for the diagnosis of dorsal infarction using the Frank vectorcardiogram AMER. HEART J 70:295 1965
10. Dower G E Horn H E. and Ziegler W G The polarcardiograph. Diagnosis of myocardial infarction, AMER. HEART J 69:369 1965
11. Binaghi G Neri G and Mazzoleni G S: L elettrocardiogramma ortogonale nell infarto del miocardio (sistema di Frank) Folia Cardiol. 24:339 1965
12. Lichtlen, P and Guhl U Zur vektorielle Analyse des Herzinfarktes, Cardiologia 49 177 1966.
13. Pipberger H V Computer analysis of electrocardiograms. Proc. of the Fifth World Congress of Cardiology Symposia Acta Cardiol (Brux) 1967 p. 486
14. Naval I A. Cosma, J and Pipberger H V Reevaluation of the Q wave in the electrocardiographic diagnosis of myocardial infarction, Med Ann. D C 36:349 1967
15. Gunnar R. M Pietras, R J Blackaller J Dadmun, S. E. Szanto, P B and Tobin J R. Jr Correlation of vectorcardiographic criteria for myocardial infarction with autopsy findings, Circulation 35:158 1967
16. Murata, K. Kurihara, H Matsushita S. Terasawa, F Ikeda, M and Seki M Usefulness and reliability of vectorcardiography in the diagnosis of myocardial infarction. A vectorcardiographic and pathologic correlation Jap. Heart J 8:522, 1967
17. Young, E. and Williams, C. The frontal plane vectorcardiogram in old inferior myocardial infarction: Criteria for diagnosis and electrocardiographic correlation, Circulation 37:604, 1968
18. Orejarena H Benchimol, A., and Dimond, E. G: The vectorcardiogram in myocardial infarction. A quantitative study of the initial 0 040 second vectors of the QRS loop using the Frank system Arch. Inst. Cardiol. Mex. 38:227 1968
19. Benchimol A Barreto E. C. and Massey B J Serial vectorcardiograms with the Frank system in patients with acute inferior all myocardial infarction, J Electrocardiol. 2:159 1969
20. Toutouzas, P Hubner P Sainani G and Shillingford J Value of vectorcardiogram in diagnosis of posterior and inferior myocardial infarctions, Brit. Heart J 31:629 1969
21. Ishikawa, K. Eddleman, E. E. Jr and Pipberger H V Electrocardiograms in pulmonary emphysema mimicking myocardial infarction. A frequent dilemma Med. Ann. D C. 39:20 1970.
22. Simonson E. Tuna, N Okamoto, N and Toshima, H Diagnostic accuracy of the vectorcardiogram and electrocardiogram Amer J Cardiol 17:829 1966.
23. Frank, E. An accurate, clinically practical system for spatial vectorcardiography Circulation 13:737 1956.
24. Langner P H Okada, R. H Moore, S. R., and Fies, H L. Comparison of four orthogonal systems of vectorcardiography Circulation 17:46, 1958.
25. Pipberger H V Computer analysis of the electrocardiogram. Computers in biomedical research New York 1965 vol. 1 Academic Press, Inc. p. 337
26. Draper H W., Peffer C J Stallmann, F W Littmann, D and Pipberger H. V The corrected orthogonal electrocardiogram and vectorcardiogram in 510 normal men (Frank lead system) Circulation 30:853 1964.
27. Pipberger H. V Goldman M J Littmann, D Murphy G. P Cosma, J and Snyder J R. Correlations of the orthogonal electrocardiogram and vectorcardiogram with constitutional variables in 518 normal men, Circulation 35:536, 1967
28. Gamboa, R. Klingeman, J D and Pipberger H V: Computer diagnosis of biventricular hypertrophy from the orthogonal electrocardiogram Circulation 39 72, 1969
29. Pipberger H. V and Eddleman, E. E., Jr: Correlation between autopsy findings and computer ECG classification in 240 cases with myocardial infarction. In prep.
30. Kerr A. J Adicoff A. Klingeman, J D and Pipberger H V Computer analysis of the orthogonal electrocardiogram in pulmonary emphysema, Amer J Cardiol. 25:34 1970.
31. Blackburn, H W Keys, A. Simonson, E. Rautaharju P and Punsar S. The electrocardiogram in population studies, Circulation 21:1160 1960
32. Kurihara, H Kuramoto, K., Terasawa, F



Fig. 1 Roentgenograms of patient with aortic ball-valve prosthesis. Films obtained in anterior posterior projection (*left*), lateral projection (*center*) and 45 degree superior elevation, 0 degree anterior elevation (*right*). The latter projection (*right*) shows aortic valve as if looking directly into orifice. Angles defined as rightward tilt and forward tilt are indicated by dotted lines.

prostheses were studied. The rightward tilt (angle between horizontal and valve orifice in frontal plane) and forward or backward tilt (angle between horizontal and valve orifice in sagittal plane) were measured in each patient (Fig. 1). From these measurements, the position necessary to obtain roentgenograms of the orifice of the prosthetic valve from a view directly above the orifice was calculated. Ideally this angle would be perpendicular to the valve orifice in both the frontal and sagittal planes. If the roentgenogram were not taken at an angle perpendicular in space to the valve orifice, the circular orifice of the valve would appear distorted in the form of an ellipse. The error that this distortion would cause in the measurement of the valve area can be calculated as described in the following paragraphs.

Let angle AOB (Fig. 2) be the rightward tilt of the orifice of an aortic valve viewed in the frontal plane. Then the elevation of the x ray tube which would be ideal to view the orifice of the valve would be on angle EOC. This angle is formed by a horizontal line EO and a line OC perpendicular to the valve orifice. If in fact, the orifice were filmed from any other angle not perpendicular to the orifice, say EOD, then any distortion on the roentgenogram would be due to viewing the orifice by an angle DOC or Δ degrees from the perpendicular. This angle of error Δ, formed between OD, the elevation at which the roentgenograms were taken, and OC, the ideal elevation for visualization of the orifice of the valve, represents the difference between an ideal and an imperfect tube elevation. The diameter of the valve would appear diminished on the film. The projection BF of the valve diameter would be visualized rather than the true diameter itself. The relationship between the true diameter of the valve, OB, and its projection, BF, can readily be calculated. Angle FBO will always equal angle DOC or Δ. The difference between the true diameter OB and the projected diameter OF caused by an improper angle Δ would be $OB - BF = OB - OB \cos \Delta = OB(1 - \cos \Delta)$. The difference between the true diameter and the projected diameter expressed as a per cent of the true diameter is

$$\frac{OB\ (1 - \cos \Delta)}{OB} \times 100 = (1 - \cos \Delta)\ 100.$$

Since it will be shown that most patients have a forward tilt of the aortic valve, one ideally should view the valve orifice from an anterior as well as rightward projection. Identical logic applies to the determination of an apparent distortion

Roentgenographic method for measurement of the cross-sectional area of the aortic valve

Paul D Stein M D
Oklahoma City Okla

An estimate of the cross-sectional area of the orifice of the aortic valve is important for the proper evaluation of patients who are potential candidates for aortic valvular surgery Hemodynamic evaluations based upon measurement of the pressure gradient across the aortic valve or calculations of the cross-sectional area of the orifice by relating the mean systolic pressure gradient systolic ejection period and cardiac output have been used with considerable success in patients with aortic stenosis.[1,2] Hemodynamic methods for the calculation of the aortic orifice area diminish in accuracy when applied to patients who have valvular regurgitation associated with narrowing because of difficulties in the estimation of regurgitant flow [3] Hydraulic equations cannot readily be applied to the measurement of the cross-sectional area of orifices narrowed less than one half normal size because the pressure gradient across such a valve is too small to measure accurately Angiographic studies supplement hemodynamic measurements for the evaluation of the aortic valve. Roentgenographic visualization of motion of the leaflets of the aortic valve calcification in the region of the aortic valve and visualization of jetting across the aortic valve give useful ancillary information that frequently correlates with the severity of the aortic stenosis.[4-7] It has not been possible however to directly measure the cross-sectional area of the aortic valve by roentgenographic methods.

The purpose of this communication is to describe a roentgenographic technique for visualization of the aortic valve as if it were viewed from directly above the orifice. This permits one to measure the orifice area and to visualize the configuration of the aortic leaflets in such a way as to show the functional anatomy The equipment necessary for this technique is readily available in many cardiac catheterization laboratories.

Methods

Preliminary studies in patients with aortic ball-valve prostheses Patients with aortic ball valve prostheses served as useful models and standards for this study Since the ring of a ball valve prosthesis is metal and therefore radiopaque, it was possible to determine with precision the spacial orientation of the aortic ring Anterior posterior and lateral roentgenograms of 31 patients with aortic ball valve

From the Departments of Medicine and Radiology University of Oklahoma School of Medicine and Veterans Administration Hospital, Oklahoma City Okla.
This project was supported by the Veterans Administration Hospital Research Service and Oklahoma Heart Association.
Received for publication July 9 1970.
Reprint requests t Paul D Stein, M.D., Veterans Administration Hospital, 921 Northeast 13th St., Oklahoma City Okla. 73104.

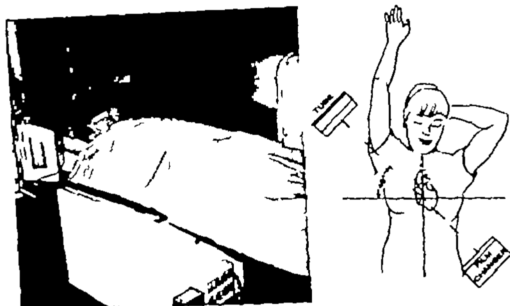


Fig. 3 Position of -ray tube and film changer utilized for visualization of orifice of aortic valve. Tube is elevated 45 degrees superiorly P tient is supine.

films by the equation $A = \frac{\pi D \; D}{4}$ Results were compared to the known cross-sectional area of each patient s prosthetic valve in order to check the accuracy of the method.

The diameters of the valve ring appeared magnified on the roentgenograms. Proper compensation for magnification was made in the calculations of valve area. Since the prosthetic valve could accurately be located on the fluoroscope the target to-object and object-to-film distance was measured with precision The nonmagnified projected diameter could be measured as follows

$$D = D \; \overline{\quad + b}$$

where D = nonmagnified projected diameter D = apparent diameter as measured on the film a = target to-object distance b = object to-film distance.

Studies in patients during cardiac catheterization. At the conclusion of the diagnostic left-sided cardiac catheterization of 21 patients, a series of films were recorded during an injection of contrast with the x-ray tube positioned at a 45 degree superior elevation in the frontal plane and a 0 degree elevation in the sagittal plane (Fig. 3) The heart was viewed approximately in a line from the right shoulder to the left pelvis. The position was identical to that used for plain films of the valve orifice of patients with prosthetic valves. Films were recorded at 4 per second on an Elema Schönander rapid film changer during the injection of 40 ml. of 75 per cent sodium and meglumine diatrizoates (Hypaque M) injected through a catheter with side holes, but no end hole. The tip of the catheter was positioned just at the aortic valve. A test injection was made prior to each power injection to be sure that the tip of the catheter was free and well away from the orifices of the coronary arteries. Contrast material was injected by a Cordis power injector at 500 psi. Film settings varied between 80 to 130 Kv and 45 to 60 Ma.sec. at one tenth of a second. Settings, of course, varied with the size of the patient. The radiographic equipment used in the study was Philips, powered by a 1 000 Ma. generator

The cross-sectional area of the aortic valvular orifice was measured from the roentgenograms by integrating the area enclosed within the valve orifice. This can be accomplished by any convenient method such as planimetry The nonmagnified projected cross-sectional area

Fig 2 Diagrammatic illustration of aortic ball-valve prosthesis. Assume x ray beam is directed across orifice, OB on any line other than perpendicular such as DO Then BF is the projection of the diameter of the orifice and equals OB cos Δ. Note angle DOC (angle Δ) and angle OBF are identical irrespective of the magnitude of Δ.

of the diameter in the sagittal plane due to imperfect anterior positioning of the x ray tube As shown above the apparent projected diameter would equal the product of the true diameter and the cosine of the angle of error between the actual x ray tube position and a true perpendicular

If the x ray tube were not positioned perpendicularly in space to the orifice of the valve then the apparent cross-sectional area of the valve as it appeared on the film would be altered The difference in area can be calculated as follows Let Δ_1 be the angle of error to the right or left of a line perpendicular to the valve orifice in the frontal plane Then as shown above the apparent diameter (D_1) would be the projection of the true diameter (D) The apparent diameter $D_1 = D \cos \Delta_1$ Let Δ_2 be the angle of error anterior or posterior to a line perpendicular to the valve in the sagittal plane. Then the apparent diameter D_2 would be the projection of the true diameter D and $D_2 = D \cos \Delta_2$ The true cross-sectional area of the circular aortic prosthetic valve is $A_T = \frac{\pi D^2}{4}$ The apparent cross-sectional area of the same valve visualized at an angle *not* perpendicular in space to the orifice would appear as an ellipse. This apparent area (A_A) is calculated by the equation

$$A_A = \frac{\pi D_1 D_2}{4} = \frac{\pi}{4} (D \cos \Delta_1)(D \cos \Delta_2).$$

The difference between the true area and apparent area is

$$A_T - A_A = \frac{\pi D^2}{4} - \frac{\pi}{4} (D \cos \Delta_1)(D \cos \Delta_2) =$$

$$\frac{\pi D^2}{4} [1 - (\cos \Delta_1)(\cos \Delta_2)]$$

This difference in area expressed as a per cent of true area is

$$\frac{A_T - A_A}{A_T} 100 = \frac{\frac{\pi D^2}{4} [1 - (\cos \Delta_1)(\cos \Delta_2)]}{\frac{\pi D^2}{4}}$$

$$\times 100 = [1 - (\cos \Delta_1)(\cos \Delta_2)]\, 100$$

From these simple trigonometrical considerations it is shown that a proper angle in space can be calculated for accurate end-on visualization of the aortic valve orifice if rightward and forward tilt are known Any deviation from a perpendicular view in space of the valve will cause a distortion of the projected valve orifice The difference between the true cross-sectional area and its distorted projection can be calculated as shown

The angle in space perpendicular to the valve orifice and necessary for perfect visualization of the orifice was calculated for each of 31 patients with ball valve prostheses. Theoretical variations of valve area due to elliptical distortion were calculated for each patient assuming that the valve had been visualized from various angles other than a true perpendicular The spacial angle that gave satisfactory results for the greatest number of patients was determined As will be discussed this was a 45 degree elevation in the frontal plane and 0 degree elevation in the sagittal plane (Fig 3)

Eighteen patients from this group of 31 were available for re-examination A roentgenogram was taken of each patient at a tube elevation of 45 degrees in the frontal plane and 0 degrees in the sagittal plane. Valve area was calcul[illegible] these

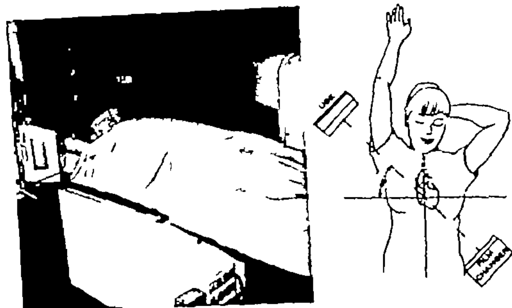


Fig. 3. Position of x-ray tube and film changer utilized for visualization of orifice of aortic valve. Tube is elevated 45 degrees superiorly. Patient is supine.

films by the equation $A = \frac{\pi D_1 D}{4}$ Results were compared to the known cross-sectional area of each patient's prosthetic valve in order to check the accuracy of the method.

The diameters of the valve ring appeared magnified on the roentgenograms. Proper compensation for magnification was made in the calculations of valve area. Since the prosthetic valve could accurately be located on the fluoroscope, the target-to-object and object-to-film distance was measured with precision. The nonmagnified projected diameter could be measured as follows:

$$D = D_A \frac{a}{a + b}$$

where D = nonmagnified projected diameter; D_A = apparent diameter as measured on the film; a = target-to-object distance; b = object-to-film distance.

Studies in patients during cardiac catheterization. At the conclusion of the diagnostic left-sided cardiac catheterization of 21 patients, a series of films were recorded during an injection of contrast with the x-ray tube positioned at a 45 degree superior elevation in the frontal plane and a 0 degree elevation in the sagittal plane (Fig. 3). The heart was viewed approximately in a line from the right shoulder to the left pelvis. The position was identical to that used for plain films of the valve orifice of patients with prosthetic valves. Films were recorded at 4 per second on an Elema Schönander rapid film changer during the injection of 40 ml. of 75 per cent sodium and meglumine diatrizoates (Hypaque-M) injected through a catheter with side holes, but no end hole. The tip of the catheter was positioned just at the aortic valve. A test injection was made prior to each power injection to be sure that the tip of the catheter was free and well away from the orifices of the coronary arteries. Contrast material was injected by a Cordis power injector at 500 psi. Film settings varied between 80 to 130 Kv and 45 to 60 Ma.sec. at one tenth of a second. Settings, of course, varied with the size of the patient. The radiographic equipment used in the study was Philips, powered by a 1 000 Ma. generator.

The cross-sectional area of the aortic valvular orifice was measured from the roentgenograms by integrating the area enclosed within the valve orifice. This can be accomplished by any convenient method such as planimetry. The nonmagnified projected cross-sectional area

was calculated from the apparent cross-sectional area by multiplying the measured area by the square of the correction factor

$$I = A_1\left(\frac{a}{a+b}\right)^2$$

where a = target to-object distance b = object to-film distance A_1 = apparent cross-sectional area of valve orifice I = non magnified projection of cross sectional area of valve orifice

The target to-object distance and object to-film distance could be accurately determined by fluoroscopy of the patient in the anterior posterior projection and observation of the tip of the catheter as it lay in the sinus of Valsalva This location was then marked over the patient's chest.

The cross-sectional area of the valvular orifice calculated in this fashion was compared to normal values values calculated by hemodynamic methods[1,2] and measurements made during open heart surgery

Results

Calculations based upon plain roentgenograms of patients with aortic ball-valve prostheses The average rightward tilt (angle AOB Fig 1) of the aortic ball valve prostheses in 31 patients was 39 degrees with a range of 6 to 60 degrees (Table I) A superior elevation of the x ray tube in the frontal plane for best visualization of the valve orifice would then be perpendicular to the valve orifice or 90 degrees plus the rightward tilt This would be angle AOC in Fig 1 or measuring in a clockwise direction from the horizontal this would be angle LOC If in each patient the x ray tube were elevated 45 degrees superiorly in the frontal plane then the angle of error Δ would be 45 degrees minus angle EOC The distortion of the projection of the diameter in the frontal plane caused by angle Δ would be $(1 - \cos \Delta)$ This was 5 per cent or less in 29 of 31 patients (Table I)

The average anterior tilt of the prosthetic valve in these 31 patients was 10 degrees with a range of plus 40 to minus 20 degrees (Table I) Six patients (19 per cent) showed a posterior tilt rather than an anterior tilt. If all films were recorded with no elevation of the tube in the sagittal plane then the distortion of the projected diameter due to a forward or backward tilt of the valve would average 5 per cent (Table I) All but 3 patients (90 per cent) would have had a distortion of the projected diameter of less than 10 per cent if films were taken with the patient supine.

The per cent error of the calculated valve area due to elliptical distortion of the projected aortic ring can be calculated from the equation $[1 - (\cos \Delta_1)(\cos \Delta_2)]$ 100 If roentgenograms of each of these 31 patients were taken at a 45 degree superior elevation and 0 degree anterior elevation, the average theoretical error in calculated valve area would have been 8 per cent. Twenty five patients (80 per cent) theoretically would show a 10 per cent error or less in valve area measured by this roentgenographic technique and 27 patients (87 per cent) would show less than a 15 per cent error (Table I)

Preliminary studies of patients with aortic ball valve prostheses The validity of this roentgenographic method for the measurement of aortic valve area was tested in 18 patients with aortic ball valve prostheses (Table II) The exact cross-sectional area of each valve was known from the patient's records. The projected orifice area was measured directly from the roentgenograms (after making proper corrections for magnification) and compared to the known area In 11 of 18 patients the measured valve area differed by 10 per cent or less from the actual orifice area In 15 patients (83 per cent) the error was 18 per cent or less. This series is small and by chance included 3 patients with uncommon spacial orientations of the valve These 3 patients predictably had inaccurate orifice measurements

In order to test the validity of the theoretical calculations of valve area the accuracy with which the orifice area could be measured from the roentgenograms was compared to the accuracy predicted by the equation $[1 - (\cos \Delta_1)(\cos \Delta_2)]$ 100 In 16 of 18 patients the per cent error predicted by this equation agreed within 10 per cent with the per cent error determined experimentally In 2 patients there were

Table I Orientation of aortic ball-valve prostheses and theoretical error in valve area calculations

Patient	Rightward tilt (degrees)	Angle EOC (degrees)	Angle Δ (degrees)	Calculated error diameter (per cent)	Anterior tilt (angle Δ_A) (degrees)	Calculated error diameter (per cent)	Calculated error valve area (per cent)
1	30	60	−15	4	20	6	10
2	40	50	− 5	1	27	11	12
3	40	50	− 5	1	10	2	3
4	39	51	− 6	1	−20	6	7
5	37	53	− 8	1	− 5	1	2
6	30	60	−15	4	10	2	6
7	60	30	15	4	17	4	8
8	56	34	11	2	16	4	6
9	50	40	5	1	15	4	5
10	55	35	15	4	−15	4	8
11	37	53	− 8	1	−12	2	3
12	45	45	0	0	6	1	1
13	57	33	12	2	40	23	25
14	35	55	−10	2	−18	5	7
15	37	53	− 8	1	15	4	5
16	42	48	− 3	1	10	2	3
17	50	40	5	1	20	6	7
18	40	50	− 5	1	22	7	8
19	35	55	−10	2	28	12	14
20	30	60	−15	4	13	4	8
21	18	72	−57	20	13	2	22
22	38	52	− 7	1	2	1	2
23	32	58	−13	3	− 5	1	4
24	35	55	−10	2	10	2	4
25	6	84	−39	22	6	1	23
26	45	45	0	0	15	4	4
27	27	63	−18	5	34	17	21
28	30	60	−15	4	15	4	8
29	52	38	7	1	21	7	8
30	30	60	−15	4	5	1	5
31	36	54	9	1	4	1	2
Average	39	51	− 6	3	10	5	8

differences of 13 and 18 per cent between the predicted and measured error (Table II).

Studies of patients during cardiac catheterization. In 21 patients, end-on views of the aortic valve were obtained on serial roentgenograms during the injection of contrast in the supra-aortic region (Tables III through V). The projection was identical to that utilized in preliminary studies of patients with ball-valve prostheses. The aortic valve frequently was shown in a strikingly clear fashion with all three leaflets well outlined in an open and closed position (Figs. 4 to 6). In patients with normal aortic valves, the valvular orifice usually appeared triangular during systole, although occasionally it appeared circular

In selected circumstances, the technique was useful even on plain films. In two patients with severe calcific aortic stenosis, it was possible to closely approximate the valvular orifice area by measuring the area circumscribed by the heavy deposits of calcium. These cases will be discussed in detail.

On the basis of clinical and hemodynamic data 9 patients were thought to have normal aortic valves. No murmur or only a Grade 1/6 systolic murmur was heard in the region of the aortic valve. No pressure gradient was measured across the aortic valve. No regurgitant flow was shown during a supra-aortic injection of contrast material. The cross-sectional area

Table II Accuracy of roentgenographic measurements of valve area in patients with aortic ball valve prostheses

Patient	Actual valve area (sq cm)	Measured valve area (sq cm)	Actual error (E_A) (per cent)	Predicted error (E_P)† (per cent)	Difference (E_A-E_P) (per cent)
1	2.2	2.3	5	−1	6
2	1.8	1.8	0	−7	7
3	2.1	1.9	−10	−5	5
4	2.1	2.3	10	−3	13
5	1.9	2.1	11	−7	18
6	1.4	1.4	0	−8	8
7	1.7	1.4	−18	−14	4
8	2.9	2.6	−10	−8	2
9	1.9	1.4	−26	−22	4
10	1.9	1.8	−5	−2	3
11	1.7	1.7	0	−4	4
12	2.3	2.3	0	−4	4
13	2.2	1.5	−32	−23	9
14	1.8	1.9	6	−4	10
15	2.1	1.5	−29	−21	8
16	1.8	1.5	−17	−8	9
17	2.3	2.0	−13	−8	5
18	1.5	1.5	0	−5	5
Average	2.0	1.8	−7	−9	7

*Negative sign indicates that measured or predicted cross-sectional area was smaller than actual area.
†From equation $[1 - (\cos \Delta_1)(\cos \Delta_2)]\,100$.

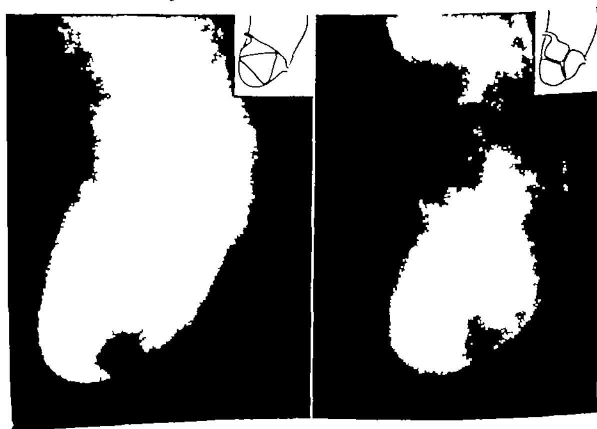


Fig. 4. Normal aortic valve visualized at an angle perpendicular to orifice. *Left,* Valve open. Triangular configuration of orifice shown diagrammatically in inset. *Right,* Valve closed. Roentgenographically measured cross-sectional area of orifice was 3.5 sq. cm.



Fig. 5 Patient with normal aortic valve Orifice appears nearly circular Roentgenographically measured area, 4.0 sq. cm. *Right*, Orifice outlined for clarity (dotted lines)

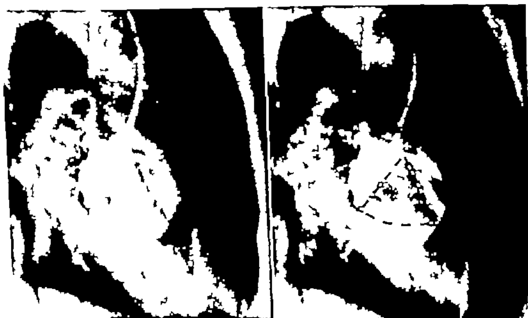


Fig. 6 Patient with mild aortic regurgitation due to Marfan syndrome. Roentgenographically measured orifice, 3.0 sq cm., appears triangular Sinuses of Valsalva appear aneurysmal. *Right*, Orifice outlined (dotted lines).

of the orifice, measured from the serial roentgenograms in eight of these patients, ranged from 3 0 to 4 5 sq cm (Table III) The measured orifice area in one patient was 1.5 sq cm In that patient configuration of the valve orifice was triangular and similar to that shown in apparently normal valves. This patient was known to have mitral stenosis. His cardiac index (2.1 L. per minute per square meter)

Table III Roentgenographic measurements of orifice area of patients with normal aortic valves

Patient	Geometric configuration of orifice	Orifice area (sq cm)	Orifice index (sq. cm./M²)
1	Triangular	3 5	2 2
2	Triangular	3 9	2 0
3	Triangular	1 5	0 8
4	Circular	4 5	2 4
5	Triangular	3 0	1 7
6	Circular	4 0	2 1
7	Triangular	3 0	2 0
8	Triangular	2 9	1 5
9	Triangular	3 8	2 0

and stroke index (27 ml per beat per square meter) were diminished It could not be stated with certainty if the diminished measured area of the valve orifice represented hemodynamically inapparent aortic stenosis incomplete opening of the valve a small but normal valve or an error in the technique of the measurement of the valve area Since none of these patients had a pressure gradient measured across the aortic valve and none were operated upon there was no way to calculate the orifice by hydraulic methods, nor was it possible to measure any of the valves directly

Six patients had mild-to-moderate aortic valvular disease characterized primarily by aortic regurgitation (Table IV) None of these patients had a peak pressure gradient across the aortic valve greater than 20 mm Hg None required surgery It was not possible to calculate the orifice area in any of these patients by hydraulic equations because regurgitant flow could not be measured accurately The roentgenographically measured areas ranged between 1 9 and 5 0 sq cm and were within the range of expected values. (The patient with the orifice area of 5 0 sq cm had aneurysmal sinuses of Valsalva and mild aortic regurgitation due to Marfan s disease) (Fig 6)

Six patients had severe aortic valvular disease with combined aortic stenosis and regurgitation Four of these patients were operated upon Roentgenographic measurements were in close agreement with measurements made at surgery (Table V)

Two of these patients had a circumferential ring of calcium around the valve that was shown on the serial films. In these 2 patients it was possible to calculate the maximum possible orifice area by measurement of the area circumscribed by the calcium These roentgenographic measurements (0 6 and 0 7 sq cm) agreed closely with measurements made during surgery (0 3 and 0 5 sq cm respectively) In 2 of these 6 patients, no anatomic correlations was possible because they did not undergo surgery Since aortic regurgitation in patients in general cannot be quantitated accurately the hydraulic equations were only of marginal value Roentgenographic measurements were of the same order of magnitude as estimates of the orifice area based upon hydraulic equations.

In one of the patients in whom there was a good correlation between roentgenographic and anatomic measurements of orifice area the roentgenograms at first glance simulated a larger than actual orifice Contrast material filled the sinuses of Valsalva and gave the appearance of a widely patent valve. Careful inspection of the films showed a fixed small orifice. Proper interpretation of the films therefore is obviously necessary

Discussion

Roentgenograms taken at the projection described in this study for the purpose of end-on visualization of the aortic valve frequently show details of the aortic valve that cannot be shown with standard pro-

Table IV Roentgenographic measurements of orifice area of patients with mild-to-moderate aortic valvular disease

Patient	Geometric configuration of orifice	Peak pressure gradient across aortic valve (mm. Hg)	Aortic regurgitation (1 to 4+)	Orifice area (sq. cm.)	Orifice index (sq. cm./M²)
1	Circular	14	3+	3.8	1.9
2	Circular	0	2+	3.1	1.8
3	Circular	10	2+	3.9	1.9
4	Triangular	0	2+	1.9	1.2
5	Triangular	20	2+	1.9	1.0
6	Triangular	0	1+	5.0	3.0

Table V Roentgenographic measurement of orifice area of aortic valves of patients with severe aortic valvular disease

Patient	Peak pressure gradient (mm. Hg)	Aortic regurgitation	Orifice area on roentgenogram	Orifice area at surgery
1	50	++	0.8	—
2	220	++	0.7	0.5
3	120	+++	0.6	0.3
4	150	+++	0.7	0.5
5	40	+++	1.5	1.8
6	38	+++	0.6	—†

*0.7 1.4 sq. cm. by hydraulic equation.
†0.8 1.6 sq. cm. by hydraulic equation.

jections. Of specific importance is the fact that all three valvular leaflets can be visualized, and their relationships to each other can be seen. The aortic valve was repeatedly and clearly shown in many patients in spite of potential problems that conceivably could have interfered with visualization, but did not seem to occur. Correlations of roentgenographic measurements with estimates of valve area based upon clinical and hemodynamic data, and correlations with measurements of the cross-sectional area of the aortic valve at surgery showed expected results.

Roentgenographic studies of patients with normal aortic valves showed particularly satisfactory results. Eight of 9 patients (89 per cent) showed orifice areas within the range of normal values. Therefore, the measurements in these patients seemed reliable. One patient had an aortic valve that clinically seemed normal although the roentgenographically measured cross-sectional area of the orifice was small (1.5 sq. cm.). That patient had severe mitral stenosis. A valve must be markedly narrowed in order to cause any accurately measurable pressure gradient across the valve. This is particularly true if cardiac output is reduced. Therefore, the unexpected observation of a moderately small valve orifice in this patient could have been a valid observation. One may also conjecture about the possibility of incomplete opening of a normal aortic valve in the presence of a diminished stroke volume. Incomplete opening, if it occurred, cannot be distinguished from a mildly stenotic valve by this roentgenographic technique.

Orifice measurements of the 6 patients with mild-to-moderate aortic valvular disease seem to be compatible with predicted results. The reliability of measurements of

orifice area in this group of patients is more difficult to assess than in the other groups of patients Valve area could not be calculated by hydraulic equations because regurgitant flow could not be quantitated The patients were not subjected to surgery

Roentgenographic measurements of the valve orifices of patients with severe aortic valvular disease characterized by a combination of stenosis and regurgitation gave valid results in each patient Two patients with heavy circumferential deposits of calcium about the valve showed calculated orifice areas strikingly close to the measurements made at surgery On the basis of measurements on the plain films taken at the projection described in this study the patients could have been spared cardiac catheterization

The results of roentgenographic measurements in patients during cardiac catheterization indicate that the method frequently gives meaningful information about the size of the orifice and the configuration of the cusps. Theoretically the method is valid According to trigonometrical calculations based upon the plain films of patients with aortic ball valve prostheses the aortic valve orifice can be measured with 90 per cent accuracy in about 8 of 10 patients. Roentgenographic measurements of the orifice area of aortic prosthetic valves when compared to the known cross-sectional area showed at least 82 per cent accuracy in 15 of 18 patients. By chance 3 patients in this small series had an uncommon spacial orientation of the valve. Therefore one could predict that in a larger series a greater number of patients could be studied with similar accuracy Furthermore any uncommon valve orientation could be readily detected during cardiac catheterization and such patients would be excluded from study by this method

As would be expected some patients are too large to permit penetration of the x ray beam on a diagonal line across the chest. The technique of contrast injection is also important for adequate visualization of the leaflets. Contrast material must be injected close to the valves. Otherwise the valvular leaflets will not be outlined Possibly by using television subtraction techniques delineation of the valve may be improved in cases in which visualization is poor Roentgenographic measurements of orifice area must be interpreted with caution in accordance with clinical and hemodynamic data. This is particularly true of patients with aortic stenosis in whom turbulent flow in the sinuses of Valsalva may simulate the appearance of a larger orifice.

Technical difficulties involved in tilting the patient or the rapid film changer during cardiac catheterization were such that a compromise projection with no anterior elevation was accepted The projection used for these studies and found by trigonometrical calculations to be adequate was one in which the tube was elevated 45 degrees superiorly in the frontal plane with the patient lying supine. The loss of accuracy with this compromise projection was minimal If the patient s head had been tilted posteriorly 10 degrees or if the tube were angled downward 10 degrees, the projection of the diameter in the sagittal plane would have more closely approximated the actual diameter in a larger number of patients. Consequently the elliptical distortion of the valve as viewed on the roentgenograms would have been somewhat diminished The spacial orientation of the valves were such that predicted distortion of the projected diameter in the sagittal plane with the patient lying supine was 5 per cent or less in 22 of 31 patients (71 per cent) 10 per cent or less in 27 of 31 patients (87 per cent) and 15 per cent or less in 29 of 31 patients (94 per cent) If the patient s head had been tilted 10 degrees posteriorly then predicted distortion of the projection of the diameter would have been 5 per cent or less in 25 of 31 patients (81 per cent) 10 per cent or less in 28 of 31 patients (91 per cent) and 15 per cent or less in all patients. Posterior tilting of the patients 15 to 20 degrees does not improve the theoretical accuracy of the measurements because the measurements of some patients would become more inaccurate as tilting increases.

Similar considerations led to the acceptance of a 45 degree superior elevation as an optimal projection in the frontal plane In this projection the diameter of

the valve in the frontal plane could be measured with an error of 5 per cent or less in 29 of 31 patients. However the remaining 2 patients would have had an error of over 20 per cent. At a superior elevation of 50 degrees no patients would show a diameter distortion in the frontal plane of over 20 per cent. However 4 would show a distortion of 6 to 20 per cent. At 55 degrees, all patients could be measured within 15 per cent accuracy It is technically difficult, however to obtain films at an angle of elevation greater than 45 degrees.

Visualization of the aortic valve from above the orifice as in Figs. 4 to 6 may help to settle a controversial problem related to the physiology of valve opening Some studies of dissected human aortic valves, attached to a pulsatile pump, and photographed from above while opening and closing, showed that the normal aortic valve orifice is triangular[8]. In contrast, other studies using model normal aortic valves, showed a circular orifice.[8-11] Roentgenographic visualization of the valves of living subjects in this study showed that both a circular and a triangular orifice may occur (Figs. 4 to 6) Both configurations seemed to be present in patients with normal as well as abnormal aortic valves.

Summary

The aortic valve in living subjects can be viewed as if looking directly into the valvular orifice by obtaining roentgenograms directed through the heart on a line approximately from the right shoulder to the left iliac crest. This roentgenographic projection (45 degree superior elevation 0 degree anterior elevation) was determined by trigonometrical calculations based upon the spacial orientation of aortic ball valve prostheses in 31 patients. Calculations based on data from these patients indicated that the aortic valve can be shown on roentgenograms taken in this projection with less than 10 per cent distortion of the cross-sectional area of the valve orifice in 8 of 10 patients. Consequently it was feasible to measure the cross-sectional area of the aortic valve by planimetry of the projected image on the roentgenograms. The method was tested in 18 patients with aortic ball valve prostheses because in such patients the precise cross-sectional area of the valve orifice was known. The roentgenographic method was at least 80 per cent accurate in 15 of 18 patients. During cardiac catheterization in 21 patients, roentgenographic measurements of the cross-sectional area of the aortic valve, using this same projection were made on serial films obtained during the injection of contrast material in the supra-aortic region. Roentgenographic measurements correlated well with clinical and hemodynamic data and direct measurements at surgery These results indicate that the cross-sectional area of the aortic valvular orifice frequently can be measured in a meaningful fashion with this method Orifice area can be measured roentgenographically in patients in whom hydraulic equations would not be applicable. Obviously roentgenographic measurements are subject to interpretation in spite of theoretical considerations based upon trigonometrical calculations. Incomplete opening of the aortic valve, due to a low stroke volume, can simulate an apparently small orifice. Eddies of contrast in the sinus of Valsalva can simulate a larger than actual orifice. In the majority of patients, this roentgenographic method of visualization of the aortic valve gives useful information regarding the cross-sectional area of the valvular orifice and the configuration of the valvular leaflets.

REFERENCES

1. Wood, P.: Aortic stenosis, Amer J Cardiol. 1:553 1958.
2. Gorlin, R., and Gorlin, S. G. Hydraulic formula for calculations of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts, Amer. Heart J 41 1 1951.
3. Gorlin, R., McMillan, I. K. R., Medd, W E., Matthews, M. B and Daley R. Dynamics of the circulation in aortic valvular disease, Amer J Med. 18:455, 1955
4. Björk, V O Cullhed, I., and Lodin, H., Aortic stenosis, correlations between pressure gradient and left ventricular angiocardiography Circulation 23:509 1961.
5. Friedenberg, M J Carlsson, E., Hartmann, A. F J and Behrer M. R. Evaluation of the degree of aortic valve stenosis by direct roentgenologic measurement of the ostium Amer. J Roentgen. 91 1347 1964.
6. Figley M M.: Angiocardiography in valvular heart disease: Morphologic and volumetric

orifice area in this group of patients is more difficult to assess than in the other groups of patients. Valve area could not be calculated by hydraulic equations because regurgitant flow could not be quantitated. The patients were not subjected to surgery.

Roentgenographic measurements of the valve orifices of patients with severe aortic valvular disease characterized by a combination of stenosis and regurgitation gave valid results in each patient. Two patients with heavy circumferential deposits of calcium about the valve showed calculated orifice areas strikingly close to the measurements made at surgery. On the basis of measurements on the plain films taken at the projection described in this study, the patients could have been spared cardiac catheterization.

The results of roentgenographic measurements in patients during cardiac catheterization indicate that the method frequently gives meaningful information about the size of the orifice and the configuration of the cusps. Theoretically, the method is valid. According to trigonometrical calculations based upon the plain films of patients with aortic ball valve prostheses, the aortic valve orifice can be measured with 90 per cent accuracy in about 8 of 10 patients. Roentgenographic measurements of the orifice area of aortic prosthetic valves, when compared to the known cross-sectional area, showed at least 82 per cent accuracy in 15 of 18 patients. By chance, 3 patients in this small series had an uncommon spacial orientation of the valve. Therefore, one could predict that in a larger series, a greater number of patients could be studied with similar accuracy. Furthermore, any uncommon valve orientation could be readily detected during cardiac catheterization, and such patients would be excluded from study by this method.

As would be expected, some patients are too large to permit penetration of the x-ray beam on a diagonal line across the chest. The technique of contrast injection is also important for adequate visualization of the leaflets. Contrast material must be injected close to the valves. Otherwise the valvular leaflets will not be outlined. Possibly by using television subtraction techniques, delineation of the valve may be improved in cases in which visualization is poor. Roentgenographic measurements of orifice area must be interpreted with caution in accordance with clinical and hemodynamic data. This is particularly true of patients with aortic stenosis in whom turbulent flow in the sinuses of Valsalva may simulate the appearance of a larger orifice.

Technical difficulties involved in tilting the patient or the rapid film changer during cardiac catheterization were such that a compromise projection with no anterior elevation was accepted. The projection used for these studies and found by trigonometrical calculations to be adequate was one in which the tube was elevated 45 degrees superiorly in the frontal plane with the patient lying supine. The loss of accuracy with this compromise projection was minimal. If the patient's head had been tilted posteriorly 10 degrees or if the tube were angled downward 10 degrees, the projection of the diameter in the sagittal plane would have more closely approximated the actual diameter in a larger number of patients. Consequently, the elliptical distortion of the valve as viewed on the roentgenograms would have been somewhat diminished. The spacial orientation of the valves were such that predicted distortion of the projected diameter in the sagittal plane with the patient lying supine was 5 per cent or less in 22 of 31 patients (71 per cent), 10 per cent or less in 27 of 31 patients (87 per cent), and 15 per cent or less in 29 of 31 patients (94 per cent). If the patient's head had been tilted 10 degrees posteriorly, then predicted distortion of the projection of the diameter would have been 5 per cent or less in 25 of 31 patients (81 per cent), 10 per cent or less in 28 of 31 patients (91 per cent), and 15 per cent or less in all patients. Posterior tilting of the patients 15 to 20 degrees does not improve the theoretical accuracy of the measurements because the measurements of some patients would become more inaccurate as tilting increases.

Similar considerations led to the acceptance of a 45 degree superior elevation as an optimal projection in the frontal plane. In this projection, the diameter of

Electrocardiographic changes due to cardiac enlargement

Kyuzo Ishikawa, M.D.
Alan S. Berson, M.S.
Hubert V. Pipberger, M.D.
Washington, D. C.

There is general agreement concerning the lack of any specific electrocardiographic (ECG) finding that indicates either the presence or the absence of congestive heart failure. However, it has often been pointed out that when recurrent heart failure has occurred, QRS amplitudes usually decrease and T waves become flat or slightly inverted. Recently, Salisbury and associates[1] experimentally revealed that congestive heart failure causes low QRS voltages together with ST-T changes in the epicardial as well as intracavitary leads. No attempt has been made, however, to relate cardiac size to ECG findings in patients with and without congestive heart failure. Therefore, a study was undertaken in an effort to establish a relationship between cardiac size estimated from chest x-ray and ECG findings during various phases of congestive heart failure as well as at a later specified time interval.

Material and methods

Using Frank corrected orthogonal lead system, the chest electrodes were placed in the fourth intercostal space. Tracings were recorded on magnetic tape and subsequently converted into digital form for further processing by a Control Data Corporation 3200 digital computer.

Recording technique and computer method detail have been reported previously. Fifteen patients with evidence of congestive heart failure were used for this study (Table I).

An orthogonal ECG (Frank lead) and a chest x-ray were obtained from each subject on the day of admission and repeated on the day that the subject's physical findings revealed either significant improvement or deterioration. The average time interval between the first and second set of tracings and x-rays was 10 days.

Cardiothoracic ratio was derived from the chest x-rays to express the cardiac size. At the time of admission, all 15 subjects exhibited (1) moderately acute distress with cardiac decompensation as evidenced by dyspnea, tachypnea, distended neck veins, hepatomegaly, and pedal edema, (2) protodiastolic gallop and/or presystolic

From the Veterans Administration Research Center for Cardiovascular Data Processing, Veterans Administration Hospital, Washington, D. C., and Georgetown University School of Medicine, Department of Medicine, Washington, D. C.

Supported in part by Grant HE 09696 from the National Heart and Lung Institute, National Institutes of Health, United States Public Health Service.
Received for publication July 13, 1970.

Reprint requests to: Dr. Kyuzo Ishikawa, Veterans Administration Hospital, 50 Irving St., N. W., Washington, D. C. 20422.

considerations, Radiol. Clin. N Amer 2:409 1964
7. Glancy J L. Freed T A O'Brien K. P and Epstein S. E.: Calcium in the aortic valve. Roentgenologic and hemodynamic correlations in 118 patients, Ann. Intern. Med. 71:245 1969
8. McMillan I K. R. Daley R. and Matthews, M B Movement of aortic and pulmonary valves studied post mortem by colour cinematography Brit. Heart J 14:42 1952.
9. Amador E. Thrower W B and Dammin G J Dynamics of normal and diseased cardiac valves, Amer. Heart J 66:777 1963
10. Bellhouse, B and Bellhouse F Fluid mechanics of model normal and stenosed aortic valves, Circ. Res. 25:693 1969
11. Bellhouse B J., and Talbot, L. The fluid mechanics of the aortic valve, J Fluid Mech. 35:721 1969

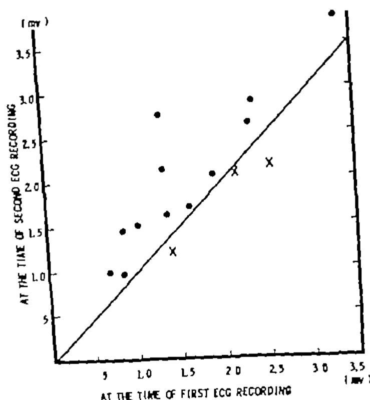


Fig. 1. Relationship between magnitude of spatial maximal QRS vector and increase in cardiac size in patients with congestive heart failure. Further cardiac enlargement with clinical deterioration, observed in 3 patients (X), was accompanied by decrease in the maximal spatial magnitude of the QRS. In the remaining 12 patients (0) the magnitude of this vector increased with decrease in cardiac size and clinical improvement.

improvement. The change in this measurement between these two stages ranged from 0.18 mv. to 2.32 mv., giving a mean of 0.74 mv., which was found statistically highly significant ($p < 0.01$). A comparable change was observed for the magnitude of maximal QRS vector in the transverse plane.

A number of other scalar and vector quantities measured were: (1) Q, R, and S amplitudes in Leads X, Y, and Z; (2) magnitude and direction of instantaneous QRS vectors at intervals of 0.01 sec.; (3) magnitude and direction of the maximal spatial P, QRS, and T vectors; (4) magnitude and direction of instantaneous QRS vectors normalized in time; (5) P and QRS duration and P-R and Q-T intervals; and (6) magnitude and direction of QRS vectors in frontal and sagittal planes.

Of all these quantities, the maximal spatial magnitude of QRS, Rx + Rz, and the magnitude of the maximal QRS vector in the transverse plane were the best ECG indicators for the clinical course of congestive heart failure.

ECG findings and heart size

The cardiothoracic ratio in 3 patients (Patients 3, 4, and 8) was greater in the more advanced stages of congestive heart failure when the second ECG tracing was taken than at the time of first ECG recording. In the remaining 12 patients, the cardiothoracic ratio was significantly smaller in the compensated (at the time of second ECG recording) than in the decompensated stage (at the time of first ECG recording) ($p < 0.01$). As shown in Fig. 2, a decrease in the cardiothoracic ratio was in all cases associated with an increase in spatial maximal magnitude of the QRS vector. The same relationship was found between the cardiothoracic ratio and both

Table I Summary of clinical and chest x ray findings

Patient	Age	Sex	Time of first tracing			Time of second tracing			Time interval between first and second tracing (day)	Clinical diagnosis
			Clinical signs of CHF	Chest x-ray		Clinical signs of CHF	Chest x-ray			
				Cardio-thoracic ratio (%)	Pulmonary vascularity		Cardio-thoracic ratio (%)	Pulmonary vascularity		
P H	78	M	++	67	++	O	61	O	2	Old MI/ASHD
M J	80	M	+++	59	+++	O	50	O	4	Old MI/HCVD
P L	35	M	++	57	++	X	61	Δ	4	Alcoholism
P O	43	M	++	53	++	X	59	\	5	PMD
A J	77	M	++	51	++	O	49	O	8	Old MI/ASHD
I W	45	M	++	51	++	O	48	O	12	Old MI/HCVD
R F	75	M	+++	55	+++	O	50	O	8	PE/ASHD
B W	40	M	++	57	++	\	00	X	12	Old MI/HCVD
R J	70	M	++	61	++	O	55	O	9	ASHD
S J	48	M	++	59	++	O	52	O	13	Old MI
R F	49	M	+++	53	+++	O	47	O	20	PMD
H H	46	M	+++	63	+++	O	51	O	18	PMD
P L	43	M	+	51	+	O	48	O	14	PMD
S C	42	M	+++	56	+++	O	50	O	9	HCVD
J A	78	M	+++	73	+++	O	65	O	14	HCVD/alcoholism

Definitions + = Mild ++ = moderate +++ = severe; O = improved; Δ = unchanged; X = worse ASHD = arteriosclerotic heart disease; HCVD = hypertensive cardiovascular disease; MI = myocardial infarction; PE = pulmonary emphysema; PMD = primary myocardial disease; and CHF = congestive heart failure.

gallop as revealed by auscultation and (3) cardiac enlargement and increased pulmonary vascular markings as demonstrated by chest x ray

ECG measurements of scalar and vector quantities are average values derived from 4 to 6 consecutive cardiac cycles analyzed by the computer

Results

The clinical and roentgenographic findings in 15 patients are summarized in Table I All patients showed moderate or severe congestive heart failure at the time of admission Three patients (Patients 3 4 and 8) were in more advanced stages of congestive heart failure when the second ECG tracing was taken In the remaining 12 patients however significant clinical improvement was noted at the time of the second ECG recording Fig 1 shows how the maximal spatial magnitude of the QRS changed according to the clinical course of patients with congestive heart failure Clinical deterioration observed in the 3 patients (Patients 3 4 and 8) was accompanied by decrease in the maximal spatial magnitude of the QRS The difference in this quantity between the two stages of the first and second ECG recordings ranged from 0 02 mv to 0.38 mv with a mean of 0 2 mv On the other hand in the remaining 12 patients, the magnitude of maximal spatial QRS vector increased with clinical improvement. The difference in this item between these two stages varied from 0 07 mv to 1 43 mv resulting in a mean of 0 43 mv This difference was statistically highly significant as demonstrated by a Student t test ($p < 0\ 01$) The sum of the R amplitudes in Leads X and Z ($Rx + Rz$) showed almost the same tendency as the magnitude of spatial QRS vectors For the 3 patients (Patients 3 4 and 8) $Rx + Rz$ was decreased at the second ECG recording as compared to that at the first ECG recording The difference in this quantity between these two stages ranged from 0 20 mv to 0 41 mv with a mean of 0 28 mv On the other hand for the remaining 12 patients this item was increased parallel to clinical



Fig. 3A. Chest x-ray of 48-year-old man with old myocardial infarction. Note the cardiac enlargement with increased pulmonary vascularity. The cardiothoracic ratio was 59 per cent. There were ventricular and atrial gallops, hepatomegaly, and pedal edema. The neck veins were distended at 45 degrees.

was decreased (Brody effect). Although this analysis was done for an infinitely extended conductor by Brody,[11] Geselowitz and Ishiwatari[12] solved this problem for a spherically bounded conductor and obtained similar results. The model used by Geselowitz consisted of 2 concentric spherical conductors with the inner one having a greater conductivity than the volume between the two. A current dipole is assumed to be located at the center of the 2 spheres. Thus, the inner sphere represents the heart cavity with its highly conductive blood while the rest of the torso is represented by a volume of considerably lower (and uniform) conductivity. The equations developed for this model clearly indicate the above mentioned effect of media of different conductivity on tangential and radial dipoles. Furthermore, if the size of the inner sphere were increased corresponding with an increase in heart size, these effects became more pronounced. The conclusions from these studies do not explain the data obtained on the patients in our study whose ECG voltages decreased with increasing heart size. The theoretical studies predict

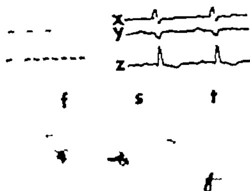


Fig. 3B. Electrocardiogram and vectorcardiogram of the 48-year-old man with old myocardial infarction (see Fig. 3A). The R amplitudes in Leads X and Z are 0.72 mv and 1.31 mv, respectively. Spatial QRS magnitude was 1.36 mv. The magnitude of QRS maximal vectors in frontal (*f*), sagittal (*s*) and transverse (*t*) planes are 0.76 mv, 1.34 mv, and 1.31 mv, respectively.

just the opposite. Therefore, one must assume that other factors are involved in the ECG changes which occur in congestive heart failure.

It is often noted that the high QRS voltages of hypertensive patients are re-

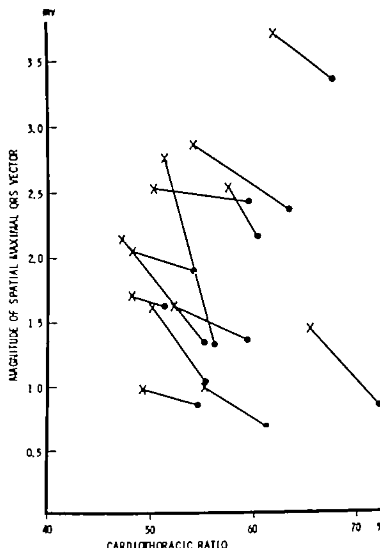


Fig. 2 Relationship between magnitude of spatial maximal QRS vector and cardiothoracic ratio. Note that the magnitude of spatial maximal QRS vectors was greater with smaller heart size than with further cardiac enlargement.

Rx + Rz and the magnitude of the maximal transverse QRS vector Figs 3 and 4 illustrate this relationship for one of the patients. In this case the magnitudes of the spatial and transverse maximal QRS vectors and cardiothoracic ratio in the decompensated stage were 1 36 mv 1 32 mv and 59 per cent while in the compensated stage these figures were 1 61 mv 1 58 mv and 52 per cent, respectively

Increase in magnitudes of the spatial and transverse maximal QRS vectors was accompanied by decrease in cardiothoracic ratio as well as by significant clinical improvement. However no statistically significant correlation was found between the degree of increase in spatial maximal magnitude of the QRS vector and the degree of decrease in cardiothoracic ratio (Fig 5) ($r = 0.27$ $p > 0.1$)

Discussion

It has long been assumed that ECG changes observed during congestive heart failure are caused by the underlying heart disease and not by the heart failure itself Schaefer[4] Geppert and Schaefer[6] and Friese[7] pointed out that patients in congestive heart failure exhibit smaller ECG potentials than when they were compensated They assumed that this ECG change was mainly due to the short-circuit effect of an increased intracavitary blood mass. The shunting effect of cardiac blood on externally measured potentials has been studied by several investigators.[8-14] A theoretical analysis of the effect of a sphere of high conductivity located close to a current dipole revealed that the effective strength of radially oriented dipoles was increased while that of tangentially oriented dipoles

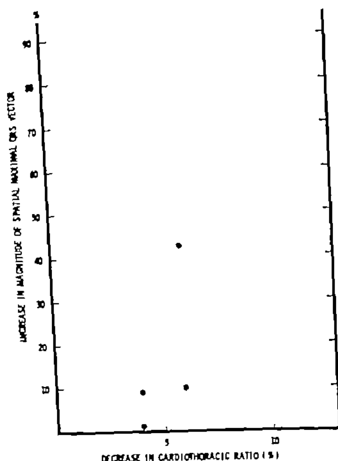


Fig. 5. Relationship between increase of magnitude of spatial maximal QRS vector and decrease of cardiothoracic ratio. No significant correlation was found between the degree of increase in spatial maximal magnitude of QRS vector and the decrease in cardiothoracic ratio ($r = 0.27$, $p > 0.1$).

the decompensated and the compensated stage. If intraventricular conduction disturbance without any accompanying prolongation of the depolarization phase were to occur, this could result in more extensive intercancellation of left and right ventricular electromotive forces. The body surface potentials might then be lower than for a normal conduction pattern. Although this possibility exists, no data are available to either confirm or reject it.

Several investigators including Horan and associates[1] and Bayley and co-workers pointed out that resistivity of the intracavitary blood mass plays an important role with regard to the body surface potential. They demonstrated that the relatively low resistivity of the intracavitary blood in anemia causes increase in voltage, and high resistivity such as in polycythemia vera tends to decrease voltage. The majority of patients in this study exhibited no significant change in either hematocrit or electrolyte level between the first and second ECG tracings. Therefore, it seems reasonable to postulate that resistivity of the intracavitary blood remained essentially unchanged in these patients.

None of the above mechanisms provides an adequate explanation for the decreased ECG potentials in patients with congestive heart failure. Despite our lack of knowledge of the underlying mechanism, however, the findings made in the present study are of some practical value in assessing the

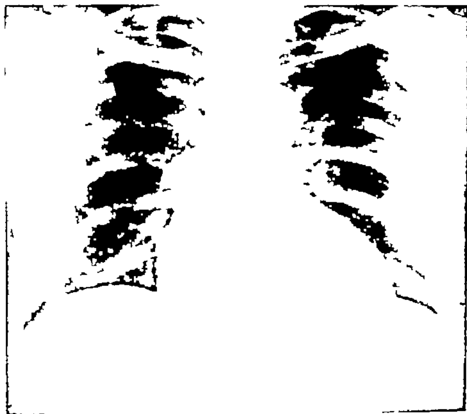


Fig 4A The same patient as in Figs. 3A and 3B 13 days after digitalization and diuresis. There was a decrease in heart size and pulmonary vascularity The cardiothoracic ratio was 52 per cent. Clinical symptoms and signs were remarkably improved

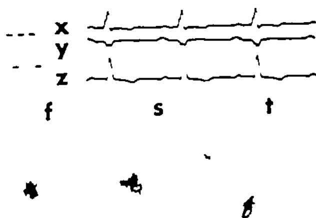


Fig 4B The same patient 13 days after digitalization and diuresis. The R amplitudes in Leads X and Z were 1 06 mv and 1 30 mv respectively The magnitude of spatial maximal QRS was increased to 1 61 mv Amplitudes of QRS maximal vectors in frontal sagittal and transverse planes were 1 11 mv 1.33 mv and 1 58 mv respectively

duced to normal or below normal voltages in ECG tracings taken after several episodes of congestive heart failure It seems reasonable to postulate that recurrent congestive heart failure over extended periods of time causes biventricular hypertrophy resulting in a decrease in body surface potential by more extensive inter cancellation of left and right ventricular electromotive forces. Since the time interval between the first and second ECG recording in this study ranged from 2 to 20 days (mean = 10 days) the ECG changes reported in this study cannot be interpreted on this basis because significant biventricular hypertrophy cannot develop within such a short period of time.

The decompensated heart could be expected to consist of more distended myocardial fibers than the normal heart Could these distended fibers produce lower action potentials than normal fibers? Dudel and Trautwein[18] using papillary muscles (cat) and Purkinje fibers (dog) clearly demonstrated that neither resting nor action potentials were affected by stretching to a tension of 100 g per centimeter beyond which irreversible injury to the fibers resulted Stretching of fibers under physiological conditions, therefore does not appear to be a plausible explanation for the ECG findings.

QRS duration for all the patients in this study was essentially unchanged between

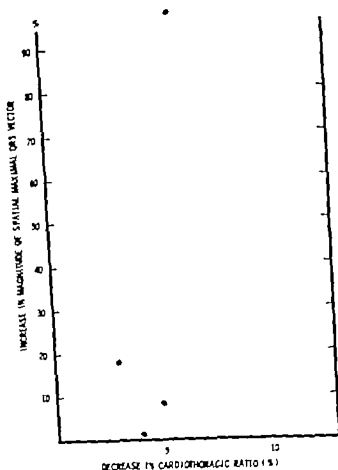


Fig. 5. Relationship between increase of magnitude of spatial maximal QRS vector and decrease of cardiothoracic ratio. N significant correlation was found between the degree of increase in spatial maximal magnitude of QRS ector and the decrease in cardiothoracic ratio (= 0.27 p > 0.1).

the decompensated and the compensated stage. If intra ventricular conduction disturbance w thout any accompanying prolongation of the depolarization phase were to occur this could result in more extensive intercancellation of left and right ventricu lar electromotive forces. The body surface potentials might then be lower than for a normal conduction pattern Although this possibil ty exists, no data are available to either confirm or reject t.

Several investigators including Horan and associates and Bayley and co-work ers pointed out that resistivity of the intracavitary blood mass plays an im portant role w th regard to the body surface potential. They demonstrated that the relatively low resistivity of the intracavitary blood in anemia causes increase in voltage, and high resistivity such as in polycythemia vera tends to decrease volt age. The majority of patients in this study exhibited no significant change in either hematocrit or electrolyte level between the first and second ECG tracings. Therefore, it seems reasonable to postulate that re sistivity of the intracavitary blood re mained essentially unchanged in these patients.

None of the above mechanisms provides an adequate explanation for the decreased ECG potentials in patients with congestive heart failure. Despite our lack of knowledge of the underlying mechanism, however the findings made in the present study are of some practical value in assessing the

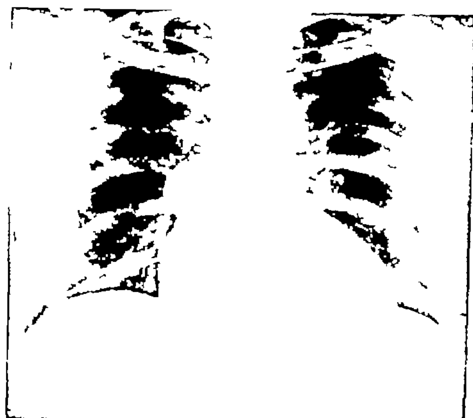


Fig 4A The same patient as in Figs. 3A and 3B 13 days after digitalization and diuresis. There was a decrease in heart size and pulmonary vascularity The cardiothoracic ratio was 52 per cent. Clinical symptoms and signs were remarkably improved.

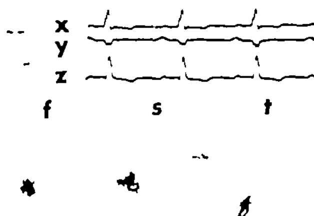


Fig 4B The same patient 13 days after digitalization and diuresis. The R amplitudes in Leads X and Z were 1 06 mv and 1 30 mv respectively The magnitude of spatial maximal QRS was increased to 1 61 mv Amplitudes of QRS maximal vectors in frontal sagittal, and transverse planes were 1 11 mv 1.33 mv and 1 58 mv respectively

duced to normal or below normal voltages in ECG tracings taken after several episodes of congestive heart failure It seems reasonable to postulate that recurrent congestive heart failure over extended periods of time causes biventricular hypertrophy resulting in a decrease in body surface potential by more extensive intercancellation of left and right ventricular electromotive forces. Since the time interval between the first and second ECG recording in this study ranged from 2 to 20 days (mean = 10 days) the ECG changes reported in this study cannot be interpreted on this basis because significant biventricular hypertrophy cannot develop within such a short period of time

The decompensated heart could be expected to consist of more distended myocardial fibers than the normal heart. Could these distended fibers produce lower action potentials than normal fibers? Dudel and Trautwein[14] using papillary muscles (cat) and Purkinje fibers (dog) clearly demonstrated that neither resting nor action potentials were affected by stretching to a tension of 100 g per centimeter beyond which irreversible injury to the fibers resulted Stretching of fibers under physiological conditions therefore does not appear to be a plausible explanation for the ECG findings.

QRS duration for all the patients in this study was essentially unchanged between

the QRS potentials in vivo, Cardiologia 12:337 1961.

12. Brody D. A. A theoretical analysis of intracavitary blood mass influence on the heart-lead relationship, Circ. Res. 4 731 1956.
13. Geselowitz, D. B., and Ishiwatari, H.: A theoretic study of the effect of the intracavitary blood mass on the dipolarity of an equivalent heart generator in Hoffman, I., and Taymore, R., editors: Vectorcardiography Philadelphia and Montreal, 1966, J. B. Lippincott Company p. 393.
14. Nelson, C. V. Chatterjee, M., and Angelakos, E. T: Further studies on the effect of the intracardiac blood of the electrocardiogram, Proc. New Eng. Cardiovasc. Soc. 16:20, 1957 1958.
15. Dudel, J. and Trautwein, W.: Das Aktionspotential und Mechanogram des Herzmuskels unter dem Einfluss der Dehnung, Cardiologia 25:344, 1954.
16. Horan, L. G., Andreae, R. L., and Yoffee, H. F.. The effect of intracavitary carbon dioxide on surface potentials in the intact canine chest, Amer. Heart J 61:504, 1961.

clinical course of congestive heart failure In patients with congestive heart failure clinical improvement as evidenced by a decrease in cardiac size was consistently accompanied by an increase in QRS voltages represented by the magnitude of the spatial maximal QRS vector Rx + Rz and the magnitude of transverse maximal QRS vector It was also found that when the patient s condition deteriorated with increase in cardiac size the QRS voltages decreased Although the reported series is relatively small there was no exception to these rules. Consequently it appears reasonable to assume that the QRS changes described above can be used as an indirect indicator of the clinical course of a patient with congestive heart failure A hypertensive patient with high QRS voltages for instance may develop normal QRS amplitudes together with signs and symptoms of congestive heart failure The ECG changes cannot be taken as a sign of clinical improvement On the contrary congestive heart failure with increasing cardiac size must be taken into serious consideration

In following up the patients of this study a correlation study was performed between the decrease in cardiothoracic ratio and the increase in the magnitude of the spatial maximal QRS vector However the correlation coefficient obtained ($r = 0.27$ $p > 0.1$) was too weak to be used for quantitative prediction of the change in cardiac size from ECG measurements. The cardiothoracic ratio has obvious limitations in expressing cardiac volume The correlation between cardiac volume and ECG measurements may be improved when more accurate measurements of increased intracavitary blood mass such as ventricular volume are employed

Summary

In following up 15 patients with congestive heart failure special effort was directed toward investigating a relationship between cardiac size estimated from chest x ray and corrected orthogonal ECG findings (Frank lead system) In 12 patients clinical improvement was accompanied by significant increase in QRS voltages represented by the magnitude of the spatial maximal QRS vector the sum of R wave amplitudes in Leads X and Z (Rx + Rz) and the magnitude of the maximal QRS vector in the transverse plane In an additional 3 patients symptoms of congestive heart failure increased with a concomitant increase in heart size In these patients, QRS voltages decreased It seems reasonable therefore to postulate that these ECG measurements can be used as an indicator of cardiac size and the clinical course of patients with congestive heart failure

It is most likely though not enough is known that intracavitary blood mass might be the cause of these ECG changes. This observation provides an additional indicator for evaluation of a patient s clinical course which can be easily obtained and monitored

REFERENCES

1 Wood P Diseases of the heart and circulation, London 1968 Eyre-Spottiswoode, p. 131
2 Salisbury P F Cross, C E Rieben, P A, and Sodi-Pallares, D Physiologic and electrocardiographic correlations in experimental left heart failure, Amer J Physiol. 209:928, 1965.
3 Frank, E. An accurate clinically practical system for spatial vectorcardiography Circulation 13:737 1956.
4 Pipberger H V Computer analysis of the electrocardiogram, in Waxman, B and Stacy R editors Computers in biomedical research, New York 1965 Academic Press, Inc., Vol. 1 p. 377
5 Schaefer H Das Elektrokardiogramm, Theorie und Klinik Berlin, Gottingen, and Heidelberg, 1951 Springer Verlag p. 67
6. Geppert M P and Schaefer H Statistische Untersuchungen uber die Beziehungen zwischen Herzgrösse und Maximalspannung von QRS im EKG Arch. Kreislaufforsch. 17:104 1951.
7 Friese, G Klinische Beobachtungen uber die Spannungsabnahme des Elektrokardiogramms bei Dilatation des Herzens, Z Kreislaufforsch. 45:99 1955
8. Nelson, C V Lange, R. L. Hecht, H. H., Carlisle, R P and Ruby A. S. Effect of intracardiac blood and of fluids of different conductivities on the magnitude of surface vectors, Circulation 14:977 1956.
9 Bayley R H Kalbfleisch, J M and Berry P M Changes in the body QRS surface potentials produced by alterations in certain compartments of the nonhomogeneous conducting model Amer. Heart J 77:517 1969
10. Nelson, C. V Chatterjee, M Angelakos, E T and Hecht H. H. Model studies on the effect of the intracardiac blood on the electrocardiogram, Amer. Heart J 62:83 1961
11 Angelakos, E. T., and Gokhan, N : Influence of venous inflow volume on the magnitude of

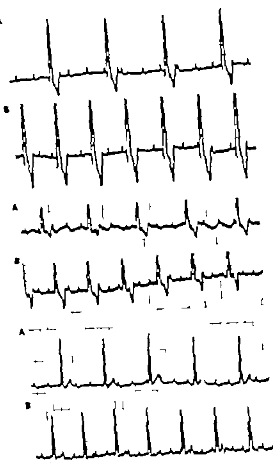


Fig. 1. Representative electrocardiographic rhythm strips from three dogs. *A* is resting rhythm and *B* is postglucagon rhythm.

[s]aturation were monitored and kept in [n]ormal ranges in the artificially ventilated [d]ogs.

Hemodynamic variables were recorded in the resting state and at frequent intervals during the hour following intravenous administration of glucagon 0.05 mg per kilogram. Atrial and ventricular rates were recorded on a Hewlett Packard 1511A electrocardiograph. Arterial and venous catheters were introduced into femoral vessels in the anesthetized dogs. Pressures were measured by Statham p23db transducers. Cardiac output was obtained by injecting indocyanine-green dye into the right atrium with sampling in the descending aorta. Outputs were calculated by standard formulas.[1] The hemodynamic data obtained from the anesthetized dogs were recorded on an Electronics for Medicine SGM recorder.

Data were statistically analyzed. The mean resting and postglucagon atrial rates, ventricular rates and cardiac outputs were compared by Student's t test for paired data. To compare data in awake versus anesthetized dogs, analysis of variance was used.

Results

Cardiac rate (Table I). The atrial rate in each dog rose significantly after administration of glucagon. The mean rate increased from 150 ± 22 to 214 ± 25 beats per minute ($p < 0.001$). This rise began within one minute after infusion and often preceded the maximal ventricular response.

Ventricular rate significantly increased from 47 ± 14 to 61 ± 15 beats per minute ($p < 0.001$). The rate rose from 40 to 58 beats per minute ($p < 0.001$) in awake animals and from 53 to 64 beats per minute ($p < 0.001$) in anesthetized dogs. The onset of chronotropic action usually began one to three minutes after infusion of glucagon. The greatest response occurred between five and fifteen minutes after drug administration with a peak at twelve minutes (Fig. 2). Though a positive ventricular response at fifty minutes was sometimes seen, the usual time course showed a return to near resting rates by thirty minutes. In only 5 of 22 experiments did glucagon cause the ventricular rate to drop; however, in each of these experiments the rate also rose above resting levels soon after the initial transient decrease.

Cardiac output (Table I). Cardiac output increased significantly from 2.1 ± 0.9 to 2.7 ± 0.9 L. per minute ($p < 0.001$). The cardiac output never dropped in response to glucagon though stroke volume fell transiently on two occasions. Maximum increments usually occurred five to ten minutes after administration of glucagon. However, in five of seven dogs tested at twenty minutes or more the cardiac output was still elevated. There was a fair time correlation between maximal ventricular rate and maximal cardiac output. However on three occasions there was a significant

[1]Kindly supplied by Dr. Gen Gie Cole, Eli Lilly and Co.

Experimental and laboratory reports

Effect of glucagon on dogs with acute and chronic heart block

Roger A. Hurwitz, M.D.
Indianapolis, Ind.

Recent studies have shown glucagon to possess cardiotonic properties when administered to the intact anesthetized dog.[1,2] These investigations have been extended to patients with normal and abnormal cardiovascular systems and have shown glucagon to possess positive chronotropic and inotropic properties.[3,4] At the same time few side effects have resulted from glucagon administration.

The effect of glucagon on dogs with complete atrioventricular heart block (AVB) has been studied on a very limited basis.[7] However, glucagon has been shown to increase cardiac output in patients with AVB and fixed rate pacemakers.[8] The purpose of this study was to more fully investigate the cardiovascular actions of glucagon on intact dogs with AVB.

Material and methods

Eleven mongrel dogs weighing 20 to 25 kilograms were studied. After being anesthetized with sodium pentobarbital (30 mg. per kilogram) the dogs were intubated and ventilated with a Harvard respirator. A right thoracotomy was performed and AVB created by injection of 10 per cent formalin into the atrioventricular node. This procedure was accomplished by piercing the right atrial wall with the injection needle, locating the atrioventricular ridge by palpation and probing for the site of the atrioventricular node by watching for electrocardiographic or direct myocardial signs of AVB. When probable contact with the nodal region was accomplished 1 c.c. of the formalin solution was injected. AVB was diagnosed according to the criteria of Massie and Walsh.[9] To exclude junctional rhythms AVB was diagnosed when the QRS configuration was irregular and greater than 0.09 second in duration (Fig. 1). In some instances serial electrocardiograms over several days were necessary to establish with certainty the completeness of the block.

Hemodynamic investigation was performed under varying conditions: (1) after chest closure on the day of the initial surgery, (2) from 1 to 8 weeks following creation of AVB in dogs anesthetized with sodium pentobarbital 20 to 30 mg. per kilogram and artificially ventilated, and (3) from 1 to 8 weeks after creation of AVB in dogs awake and standing quietly in harness. Arterial blood pH and oxygen

From the Division of Pediatric Cardiology, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Ind.

Supported by research grants from the James Whitcomb Riley Memorial Association and in part with facilities provided by Heart Program Project Grant HE-6308-09 from the National Heart Institute, National Institutes of Health, and by United States Public Health Service Grant RR-00162 in support of statistical computation.

Received for publication May 21, 1970.

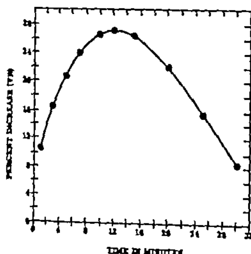


Fig. 2. Average per cent increase in ventricular rate (VR) versus time elapsed after glucagon administration in all dogs tested.

strated a glucagon-induced cardiac rate increase in dogs with atrioventricular nodal rhythm. Therefore it seemed wise to investigate further the effects of glucagon on dogs with AVB.

Glucagon in lower doses than used here,[3] is known to produce cardiotonic effects in dogs. However 0.05 mg per kilogram was selected as a standard since it has been an effective and safe dose in man. Furthermore, similar doses have been safely administered to infants for treatment of hypoglycemia.[18] The glucagon administered in this study caused a marked rise in atrial rate in each case, so that any lack of positive ventricular response could be attributed to AVB.

The results herein show a significant rise in ventricular rate of 30 per cent. This relative increase is similar to data previously accumulated in dogs with normal conducting systems.[11, 12] The increment in awake dogs of 42 per cent was almost twice the 23 per cent rise found in anesthetized animals. However maximal rates after glucagon administration were more similar. The early maximal response (2 to 12 minutes) and the duration of action (20 minutes) are comparable to dogs without AVB.[13] Cardiac output rose 29 per cent, which was similar to the increase previously found in humans without AVB and in those with fixed-rate pacemakers.[4-6, 8] This augmented cardiac output occurred

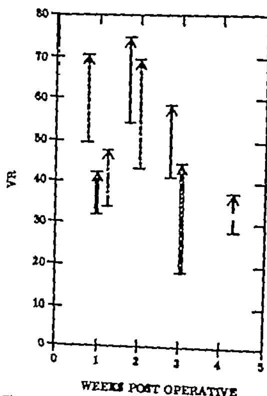


Fig. 3. Ability to change in ventricular rate (VR) after glucagon administration in four dogs tested more than once while awake. The same dog is represented by the same symbols.

early usually within five minutes after administration of glucagon. A smaller elevation of cardiac output persisted for periods beyond twenty minutes. Repeatability of ventricular rate response, both during the same experimental run and on a chronic basis, was documented in this study. Cardiac output and ventricular rate response were often parallel. However stroke volume usually increased in response to glucagon. Glick and associates[3] have previously shown glucagon-induced enhancement of contractility in dogs with heart rates kept constant by pacing. Cardiac output has also been shown to increase in patients with fixed-rate pacemakers.[4] Thus glucagon may act through different pathways in producing chronotropic and inotropic responses.

The exact mechanism of action of glucagon is not yet known. Glucagon effect is probably not mediated through catecholamines, since beta adrenergic receptor blockade with propranolol has not altered glucagon's action.[1,2,11,14] In the present ex

*Table I Resting and post glucagon data on all dogs**

Dog	Week post operative	Anesthesia	Rest			Glucagon		
			Atrial rate	Ventricular rate	Cardiac output (L./min.)	Atrial rate	Ventricular rate	Cardiac output (L./min.)
8	3	−	200	45		210	68	
8	6	+	160	62	2.8	210	80	2.9
9	0	+	170	60	1.2	250	62	1.5
9	2	−	170	54		200	74	
9	3	−		41			58	
10	0	+	190	57	2.5	230	74	3.3
10	1	−	150	40		190	59	
12	2	+	190	80	1.9	230	94	2.5
15	0	+	200	60	1.3	230	70	2.0
16	0	+	150	50	1.3	200	66	2.5
16	1	−	150	48		170	70	
16	2	−	120	43		160	68	
16	6	+	140	54	1.4	190	62	2.0
18	0	+	170	40	1.9	220	46	2.1
20	1	−	160	33		220	42	
20	3	+	140	34	2.5	200	44	3.5
20	4	−	145	26		230	44	
21	0	+	170	72	3.5	210	84	3.7
21	1	−	140	42		200	52	
21	6	+	150	41	3.8	210	48	4.6
22	1	−	150	34		230	47	
22	2	+	130	48	1.5	250	58	2.0
22	4	−	170	28		260	37	
22	6	+	130	50	1.7	220	56	2.7

*Atrial rates, ventricular rates, and cardiac output values are maximum determinations.

increase in heart rate without an elevation in stroke volume.

Effects of duration of AVB The chronicity of AVB did not hinder the dogs response to glucagon AVB of longer duration usually produced lower resting ventricular rates in the same dogs when awake but the relative rate increment due to glucagon was virtually unchanged (Fig 3) Cardiac output rose significantly in three dogs given glucagon six weeks after production of AVB (Fig 4) Also doses of glucagon repeated 60 minutes apart produced comparable or increased increments in ventricular rate and cardiac output in three dogs.

Effects on cardiac rhythm In the majority of experiments (12 of 22) the cardiac rhythm remained constant after glucagon administration On four occasions extraneous ventricular foci were diminished An entirely new focus was established for short periods of time (maximum 7 minutes) in six experiments. In addition there was more variance in pacemaker site than before drug administration on two occasions. A short burst of ventricular tachycardia (lasting 3 to 15 seconds) occurred twice, and transient atrial flutter occurred in one experiment.

Adverse effects Except for the previously mentioned changes in cardiac rhythm no definite deleterious effects were noted. Blood pressure remained stable. No deaths were attributable to glucagon in this study

Discussion

This study further investigates the cardiovascular effects of glucagon on dogs with complete AVB One previous investigation has shown three dogs with AVB to have no significant ventricular rate change after glucagon administration[7] Lucchesi and co-workers[11] demon

Cardiovascular effects of glucagon in man, Canad. Med. Ass. J 98 1161 1968.

4. Parmley W W Glick, G. and Sonnenblick, E. H. Cardiovascular effects of glucagon in man, New Eng. J Med. 279 12, 1968.
5. Linhart, J W Barold, S. S Cohen, L. S., Hildner F J and Samet, P Cardiovascular effects of glucagon in man, Amer J Cardiol. 22 706, 1968.
6. Williams, J F J Childress, R. H., Chip, J N and Border J F Hemodynamic effect of glucagon in patients with heart disease, Circulation 39:38, 1969
7. Steiner C., Wit, A. L and Damato, A. N Effects of glucagon on atrio-ventricular conduction and ventricular automaticity in dogs, Circ. Res. 24 167 1969
8. Ashley W W Kaminsky D M Lipski, J I Weisensel, A. C Donoso, E., and Friedberg, C. K. Hemodynamic effects of glucagon in patients with fixed-rate pacemakers, Amer J Cardiol 25:82, 1970.
9. Massie, E., and Walsh, T J Clinical vector cardiography and electrocardiography Chicago, 1960, Year Book Medical Publishers, Inc., p. 452.
10. *Hamilton, W F., The physiology of the cardiac* output, Circulation 8:527 1953.
11. Loerbel, B. R., St tz, D. R., and Winfeld, R. A. Glucagon, its enhancement of idioventricular nodal pacemaker activity and failure to increase ventricular automaticity in dogs, Circ. Res. 25 183 1969
12. Barnett, H. L. Pediatrics, New York, 1968, Appleton-Century-Crofts, Inc.
13. Lipski, J I. Kaminsky D M and Friedberg, C. K. The electrophysiologic properties of glucagon on the normal canine heart, Amer J Cardiol. 23 124 1969
14. Levey G. S., and Epstein, S. E.: Activation of adenyl cyclase by glucagon in cat and human heart, Circ. Res. 24 151 1969

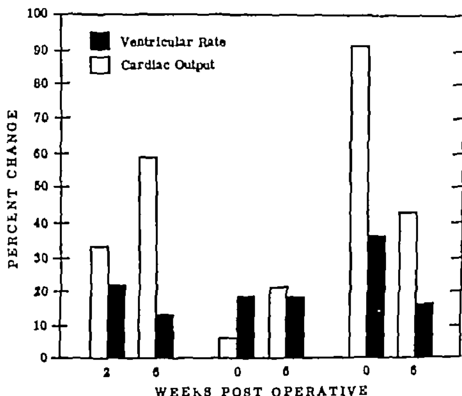


Fig 4 Per cent change in ventricular rate and cardiac output after glucagon administration in three anesthetized dogs tested at least four weeks apart.

periment administration of MJ 1999 a potent beta adrenergic blocking agent caused marked bradycardia followed by asystole on two occasions. This effect was abolished by immediate administration of glucagon In addition the asystole produced in two dogs with AVB by intravenous administration of high doses of lidocaine was terminated by glucagon Thus, it would seem that the cellular anesthetic properties of lidocaine were antagonized or abolished by the action of glucagon

Glucagon has not yet been used clinically to treat complications of AVB Since the drug increases ventricular rate and cardiac output, has a rapid onset and relatively long duration of action and infrequently produces further arrhythmia glucagon has a potential usefulness in the treatment of symptomatic AVB This agent could be employed in the acute phase of AVB or during insertion of an artificial pacemaker Glucagon might also be used for augmenting cardiac output when advanced heart block precludes administration of digitalis. The drug may also benefit subjects suffering from digitalis or propranolol toxicity resulting in bradycardia. Since glucagon has already been safely administered to children suffering from hypoglycemia, it may have special merit in the treatment of infants and children with cardiac problems.

Summary

The effects of glucagon on dogs with complete atrioventricular heart block (AVB) was investigated Significant increases in atrial rate, ventricular rate and cardiac output resulted from glucagon administration This agumentation was found to be repetitive in dogs with chronic AVB The early onset of action duration of response and relative lack of adverse effects would suggest that glucagon might be a valuable drug in the treatment of symptomatic heart block.

REFERENCES

1 Lucchesi, B R. Cardiac actions of glucagon, Circ. Res. 22 777 1968.
2 Glick, G Parmley W W Wechsler A. S., and Sonnenblick E. H. Glucagon Its enhancement of cardiac performance in the cat and dog and persistence of its inotropic action despite beta-receptor blockade with propranolol, Circ. Res. 22 789 1968.
3 Klein, S. W Morch, J E. and Mahon, W A.

Cardiovascular effects of glucagon in man, Canad. Med. Ass. J. 98:1161, 1968.
4. Parmley, W. W., Glick, G., and Sonnenblick, E. H.: Cardiovascular effects of glucagon in man, New Eng. J. Med. 279:12, 1968.
5. Linhart, J. W., Barold, S. S., Cohen, L. S., Hildner, F. J., and Samet, P.: Cardiovascular effects of glucagon in man, Amer. J. Cardiol. 22:706, 1968.
6. Williams, J. F., Jr., Childress, R. H., Chip, J. N., and Border, J. F.: Hemodynamic effects of glucagon in patients with heart disease, Circulation 39:38, 1969.
7. Steiner, C., Wit, A. L., and Damato, A. N.: Effects of glucagon on atrio-ventricular conduction and ventricular automaticity in dogs, Circ. Res. 24:167, 1969.
8. Ashley, W. W., Kaminsky, D. M., Lipski, J. I., Weisenseel, A. C., Donoso, E., and Friedberg, C. K.: Hemodynamic effects of glucagon in patients with fixed-rate pacemakers, Amer. J. Cardiol. 25:482, 1970.
9. Massie, E., and Walsh, T. J.: Clinical vectorcardiography and electrocardiography, Chicago, 1960, Year Book Medical Publishers, Inc., p. 452.
10. Hamilton, W. F.: The physiology of the cardiac output, Circulation 8:527, 1953.
11. Lucchesi, B. R., Stutz, D. R., and Winfield, R. A.: Glucagon, its enhancement of atrioventricular nodal pacemaker activity and failure to increase ventricular automaticity in dogs, Circ. Res. 25:183, 1969.
12. Barnett, H. L.: Pediatrics, New York, 1968, Appleton-Century-Crofts, Inc.
13. Lipski, J. I., Kaminsky, D. M., and Friedberg, C. K.: The electrophysiologic properties of glucagon on the normal canine heart, Amer. J. Cardiol. 23:124, 1969.
14. Levey, G. S., and Epstein, S. E.: Activation of adenyl cyclase by glucagon in cat and human heart, Circ. Res. 24:151, 1969.

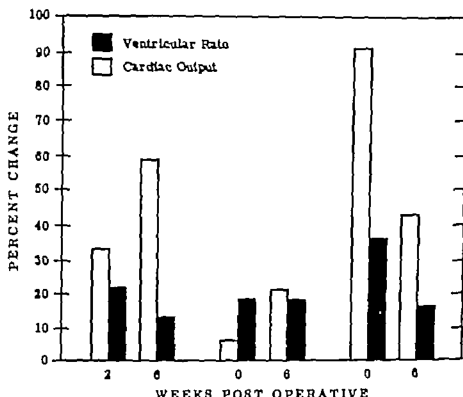


Fig 4 Per cent change in ventricular rate and cardiac output after glucagon administration in three anesthetized dogs tested at least four weeks apart.

periment administration of MJ 1999 a potent beta adrenergic blocking agent caused marked bradycardia followed by asystole on two occasions. This effect was abolished by immediate administration of glucagon In addition the asystole produced in two dogs with AVB by intravenous administration of high doses of lidocaine was terminated by glucagon Thus it would seem that the cellular anesthetic properties of lidocaine were antagonized or abolished by the action of glucagon

Glucagon has not yet been used clinically to treat complications of AVB Since the drug increases ventricular rate and cardiac output, has a rapid onset and relatively long duration of action and infrequently produces further arrhythmia glucagon has a potential usefulness in the treatment of symptomatic AVB This agent could be employed in the acute phase of AVB or during insertion of an artificial pacemaker Glucagon might also be used for augmenting cardiac output when advanced heart block precludes administration of digitalis. The drug may also benefit subjects suffering from digitalis or propranolol toxicity resulting in bradycardia. Since glucagon has already been safely administered to children suffering from hypoglycemia it may have special merit in the treatment of infants and children with cardiac problems.

Summary

The effects of glucagon on dogs with complete atrioventricular heart block (AVB) was investigated Significant increases in atrial rate ventricular rate and cardiac output resulted from glucagon administration This agumentation was found to be repetitive in dogs with chronic AVB The early onset of action duration of response and relative lack of adverse effects would suggest that glucagon might be a valuable drug in the treatment of symptomatic heart block.

REFERENCES

1 Lucchesi B. R. Cardiac actions of glucagon Circ. Res. 22:777 1968.
2. Glick, G Parmley W W., Wechsler A. S. and Sonnenblick E. H Glucagon Its enhancement of cardiac performance in the cat and dog and persistence of its inotropic action despite beta-receptor blockade with propranolol, Circ. Res. 22:789 1968
3 Klein, S. W Morch J E. and Mahon W A.

SF 1 transducer tipped catheter in the left ventricle and the first derivative of the pressure pulse determined by an RC differentiator (Sanborn 350-16). Pressures were recorded with a Sanborn Model 560 photographic recorder. All pressure measurements were averaged through two respiratory cycles. LVEDP was recorded with a sensitivity such that 1.0 mm. Hg equaled a 1.0 mm. paper deflection. Cardiac output was determined by a standard indicator dilution technique using indocyanine green. The withdrawn blood was reinfused immediately.

Following completion of the basal pressure and cardiac output measurements, blood was withdrawn for serum electrolytes. A superficial neck muscle was biopsied and a portion weighed immediately and frozen in a small volume of distilled water for later potassium analysis.

In order to assess the animal's response to a chronotropic and inotropic stimulus, isoproterenol was infused at a rate of 0.2 µg per kilogram per minute for 10 minutes. Left ventricular pressure and LV dp/dt were recorded during the last minute of infusion. Following this infusion no further measurements were made for 30 minutes.

Ventricular function curves were obtained by infusing dextran 70,* a 6 per cent solution in normal saline, at the rate of 1.75 to 2.3 ml. per kilogram per minute over a 15 to 20 minute interval. LVEDP, right atrial pressure, aortic pressure, and cardiac output were recorded initially and then every 3 minutes during the infusion. This volume of dextran produced a LVEDP of at least 20 mm. Hg and a right atrial pressure of 7 mm. Hg or more.

Eight of the animals so studied were returned to metabolic cages. They were given a dog pellet potassium deficient diet (General Biochemicals No. 70540) which provided about 6 mEq. of potassium per day and the drinking water was prepared using distilled water and adding NaCl to make a 0.1 per cent solution, thereby insuring an adequate sodium intake. The animals were given desoxycorticosterone acetate, 25 mg. subcutaneously every 5 out of 7 days. Six animals survived 2 weeks of this potassium-depleting regimen and were restudied as initially outlined. The 24 hour urine volumes were recorded and aliquots analyzed for potassium concentration.

Following their initial catheterization a second control group of 5 dogs received an identical diet and dosage of desoxycorticosterone. However, their 0.1 per cent sodium chloride drinking water also contained 1.7 per cent KCl which provided about 150 mEq. of potassium per day. Urine specimens were not analyzed for potassium. Repeat studies, as outlined above, were performed after 2 weeks.

At the completion of the second study the animals were put to death. Biopsies of the left ventricular free wall and anterior papillary muscle were obtained for histologic study. A small portion of left ventricular muscle was weighed, frozen in distilled water, and later analyzed for potassium.

Sodium and potassium were determined by flame photometry. Muscle potassium determinations were performed using the method of Seta and co-workers[4] and are expressed as mEq. of potassium per kilogram of wet weight. Serum magnesium was measured by the method of Dawson and Heaton.[5]

Mean systolic ejection rate (MSER) in milliliters per second was calculated by the formula, MSER = SV/SEP, where SV equals stroke volume in milliliters and SEP is the systolic ejection period in seconds as determined from the aortic pressure tracing recorded at 75 mm. per second. Left ventricular stroke work (LVSW) and minute work (LVMW) were calculated by standard formulas. Initial and restudy values were compared at the LVEDP of 20 mm. Hg, a level at which the curves begin to plateau.

Statistical analysis of the observed differences between the initial and restudy observations was performed using the Student t test.

Results

All the potassium-depleted animals exhibited weakness, polyuria, and anorexia by the tenth to twelfth day of the potassium-depleting regimen. Two animals died after demonstrating the above signs and biopsies of their cardiac muscle were ob-

*Dextran, in contrast to saline, results in a sustained increase in intravascular volume and thereby provides sufficient time for serial indicator dilution curves.

Cardiovascular function in potassium depleted dogs

Robert C Bahler M.D
Louis Rakita M D
Cleveland Ohio

Effects of various cations on myocardial contractility have been studied primarily by varying their concentration in the perfusate of either isolated cardiac muscle or heart-lung preparations Such acute experiments have shown enhanced contractility in the presence of low potassium concentrations.[1,2] Whether chronic K^+ loss produces a similar result is unknown Prior studies of chronic potassium depletion have focused on alterations in cardiac electrical activity and myocardial histology rather than hemodynamics The purpose of this report is to indicate the changes in cardiovascular function which occur with chronic potassium depletion in more intact preparations than have previously been employed

Methods

Thirteen mongrel dogs weighing 9 to 18 kilograms were anesthetized 24 hours post prandially with pentobarbital 25 mg per kilogram The animals were intubated and ventilation was controlled with a Harvard respiratory pump Body temperature was maintained within 1 C of 37° C by use of a heat lamp The chest was not opened The left femoral vein and artery and left carotid artery were isolated and cardiac catheters placed in the right ventricle left ventricle and the distal aortic arch Patency of the catheters was maintained by intermittent flushing with a heparinized saline solution The animals received additional anesthesia at the rate of 4 to 5 mg per kilogram per hour All measurements were begun two and one-half hours after induction when further decline of cardiac output after pentobarbital is not significant [3]

Right heart and aortic pressures were measured through 7F Cournand catheters connected directly to Statham P23AA gauges. Left ventricular pressure was recorded through an 8F 50 cm Goodale-Lubin catheter connected to a Statham P23Db gauge a system which provides adequate frequency response for accurate recording of left ventricular end diastolic pressure (LVEDP) at rapid heart rates. Zero pressures were obtained with the gauges attached to the dog carriage, thereby assuring identical zero pressure levels during restudy The position approximated the mid-chest level Left ventricular maximal rate of pressure rise (LV dp/dt) was measured by placing a Statham

From the Department of Medicine of Case Western Reserve University School of Medicine at Cleveland Metropolitan General Hospital and the Veterans Administration Hospital.
This study was supported by grant from the American Heart Association, Northeast Ohio Chapter, and in part by United States Public Health Service Grant No. HE09769
Received for publication June 26, 1970.
Reprint requests to: Dr. Bahler Cardiology Section, Veterans Administration Hospital, 10701 East Boulevard, Cleveland, Ohio 44106.

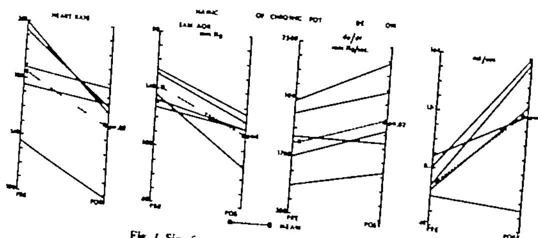


Fig. 1 Significant hemodynamic changes are illustrated.

There was no significant weight change in either the experimental or control animals. Serum magnesium levels were not significantly altered in either group (Table I)

Electrocardiographic changes Prolongation of the Q-T interval was evident in all potassium-depleted animals and U waves were prominent in several (Table II)

Heart rate The average resting sinus rate under Nembutal anesthesia decreased from 186 per minute to 152 per minute following potassium depletion (Fig 1) The control group did not show any change in resting rate (Table II)

The maximum rate during Isuprel infusion was significantly lower in the experimental group and unchanged in the controls (Table II)

Mean arterial pressure and systemic vascular resistance Mean arterial pressure fell in all potassium-depleted dogs. The control animals had a slight decline in arterial pressure but it was not significant (Fig 1) The resting systemic vascular resistance fell markedly in three depleted animals and did not change significantly in the remaining experimental or control animals (Table II) Mean arterial pressure and systemic vascular resistance were consistently lower during ventricular function curves in 4 of the 5 potassium-depleted dogs.

Intracardiac pressures As noted in Table II apart from the lower left ventricular systolic pressure there was no significant change in the intracardiac pressures following potassium depletion.

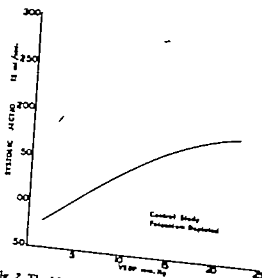


Fig. 2 The LVSW increased at all levels of LVEDP in this K depleted animal.

Maximum rate of rise of left ventricular pressure There was a significant increase in LV dp/dt after potassium depletion (Fig 1) During Isuprel infusion LV dp/dt rose similarly in the potassium-depleted and control dogs (Table II)

Mean systolic ejection rate. A significant increase in resting MSER occurred in the experimental animals but not in the controls (Fig 1 Table II) Ejection times remained constant. The mean systolic ejection rates observed during ventricular function curves were increased in 4 dogs after potassium depletion (Table II Fig. 2) The experimental animal with no increase in MSER also showed no fall in

*Table I Serum and muscle electrolytes**

Variables	Potassium depleted		Control	
	Initial	Restudy	Initial	Restudy
Serum K (mEq./L.)	3.60 ± 0 0	2.20 ± 0.30‡	3.60 ± 0.40	3.40 ± 0.40
Serum Na (mEq./L.)	151.00 ± 7.00	157.00 ± 6.00	155.00 ± 5.00	158.00 ± 6.00
Serum Mg^{++} (mEq./L.)	1.29 ± 0.16	1.46 ± 0.36	1.28 ± 0.16	1.49 ± 0.37
Cardiac muscle K (mEq./kilo wet wt.)	86.00 ± 6.00†	79.00 ± 5.00		83.00 ± 3.00
Skeletal muscle K (mEq./kilo wet wt.)	90.00 ± 8.00	73.00 ± 8.00§	90.00 ± 9.00	84.00 ± 3.00

*Mean values ± 1 S.D.
†Based on 5 normal dogs from noncardiac studies.
‡p = 0.001
§p = 0.02

Table II Cardiovascular effects of potassium depletion

Variables	Potassium depleted			Control		
	Initial	Restudy	Mean difference	Initial	Restudy	Mean difference
Resting heart rate	186.00	152.00	−34.00 ± 10.40*	171.00	170.00	+1.00 ± 22.00
Heart rate with isoproterenol	230.00	188.00	−42.00 ± 8.00†	197.00	206.00	+9.00 ± 22.00
Corrected Q-T time	0.32	0.41	+0.07 ± 0.01‡	0.37	0.36	−0.01 ± .04
Cardiac output (L./min.)	2.03	2.50	+0.50 ± 0.50	2.03	2.02	−0.01 ± .30
Stroke volume (c.c.)	10.60	15.30	+4.70 ± 2.30	11.20	11.90	+0.70 ± 2.00
Mean aortic pressure (mm. Hg)	139.00	113.00	−26.00 ± 3.50	130.00	123.00	−7.00 ± 6.00
Systemic vascular resistance units	72.00	60.00	−12.00 ± 15.00	71.00	68.00	−3.00 ± 9.00
LV dp/dt (mm. Hg/sec.) resting	1,846.00	2,130.00	+1,284.00 ± 115.00‡	1,730.00	1,735.00	+5.00 ± 83.00
LV dp/dt (mm. Hg/sec.) with isoproterenol	3,016.00	3,080.00	+73.00 ± 210.00	2,803.00	2,739.00	−64.00 ± 450.00
LVEDP (mm. Hg)	2.00	3.00	+1.00	4.00	5.00	+1.00
Right atrial pressure (mm. Hg)	2.00	2.00	0	1.50	2.00	+0.50
Ejection time seconds	0.12	0.12	0	0.10	0.10	0
MSER (ml./sec.) resting	70.00	121.00	+51.00 ± 17.00§	103.00	105.00	+2.00 ± 12.00
MSER (ml./sec.)‖	137.00	266.00	+129.00 ± 35.00	177.00	225.00	+48.00 ± 28.50
LV stroke work (Kg.-M)‖	37.50	52.00	+14.50 ± 5.00§	51.00	52.20	+0.60 ± 8.90
LV minute work (Kg.-M)‖	6,330.00	8,220.00	+1,440.00 ± 723.00	7,640.00	8,740.00	+1,100.00 ± 1,770.00

± = 1 S.E. of the mean.
*p = 0.02
†p = 0.01
‡p = 0.05
‖Compared at LVEDP of 20 mm. Hg during ventricular function curves.

tained. One animal maintained a constant ventricular bigeminal rhythm during restudy and is therefore not included in the analysis of hemodynamic data.

The average measured urinary potassium loss of the 5 restudied animals was 72 mEq. The 2 animals which died prior to restudy had a similar potassium loss. Potassium depletion was further evidenced by the reduction in serum and skeletal muscle potassium concentrations (Table I).

The 5 control animals exhibited none of the signs of hypokalemia and all survived. Despite receiving about 150 mEq. of potassium per day, the serum, skeletal, and cardiac muscle potassium concentrations were slightly, although not significantly, reduced (Table I).

preparations.[23] Similarly a rapid infusion of potassium solutions into the coronary arteries of intact animals produced a transient depression of cardiac contractility.[24]

Moderate potassium deficiency produced in 3 normal humans by administering chlorthiazide for one week reduced the serum potassium concentration 33 per cent, but erythrocyte and body potassium was reduced only 7 per cent. These changes led to electrocardiogram (ECG) evidence of hypokalemia and a feeling of weakness. However quantitated stress exercise was performed at similar heart rates and levels of subjective fatigue before depletion, during depletion and following repletion.[25] Interestingly the duration of mechanical systole shortened during the hypokalemic state this suggests an increased MSER a finding similar to that noted in our potassium-depleted dogs.

In a study of the effects of chronic potassium depletion upon the action of acetyl strophanthidin the depleted animals had a slower resting heart rate. Depletion was achieved by dietary deprivation Goodyer and associates induced acute hypokalemia in two animals using hemodialysis, and the heart rate fell. Similar changes were noted in our potassium-depleted animals their resting cardiac rate during anesthesia was lower and a chronotropic stimulus was less effective.

The impaired chronotropic response could be explained by a prolonged action potential since Lieberman[1] observed prolonged action potentials when chick heart cells were cultured in a hypokalemic nutrient bath. He also demonstrated that a hypokalemic nutrient increases the rate of diastolic depolarization a change which should increase the pacemaker rate. Nevertheless, the pacemaker rate of the cultured cells was reduced by hypokalemia, suggesting that prolonged action potential was the dominant influence of hypokalemia.

Studies of Purkinje fiber action potentials have confirmed that a low extracellular K^+ concentration produced a prolonged action potential and enhancement of diastolic depolarization With low extracellular K^+ the Purkinje fibers actually developed pacemaker characteristics, which may in part explain the ectopic rhythms associated with hypopotassemia. In contrast, a pacemaker such as the sinus node with a higher intrinsic rate appears to be slowed by hypokalemia prolongation of the action potential is then the principal effect of hypopotassemia.

The reduced arterial pressure at rest and during ventricular function curves in our potassium-depleted dogs was secondary to a fall in systemic vascular resistance, implicating a reduced arteriolar muscle tension Potassium depletion is known to decrease smooth muscle tone in the gut and bladder Arteriolar smooth muscle may respond similarly since hypotension also appeared in potassium-depleted rats.[19] Moreover isolated vascular smooth muscle developed less tension when studied in a hypokalemic bath,[20] thus suggesting a direct effect on vascular smooth muscle and not just depressed neuromuscular transmission The contractility of vascular smooth muscle, in contrast to cardiac muscle, is adversely affected by potassium depletion.

Absence of light microscopic changes in the cardiac muscle of the potassium-depleted dogs has been previously reported.[21,22] In contrast, human cardiac muscle exhibits histologic changes in association with severe chronic potassium deficiency.[23-26] Cardiac necrosis has readily been produced in the potassium-deficient rat.[21,22] Initial histologic changes in the electrolyte-steroid-cardiopathy" occur after about one week of potassium depletion and are followed by more extensive electro-microscopic changes.[23] The frequency and severity of histologic changes in rat myocardium are primarily related to the severity and not to the duration of the potassium-deficient state.[21,27] Lesions are evidenced when the myocardial K^+ falls below 72 mEq per kilogram wet weight.[27] This observation may explain the difficulty in inducing similar histologic changes in the dogs. Profound skeletal muscle weakness and anorexia result in death prior to a reduction of myocardial potassium to this range. The lowest cardiac potassium concentration we observed was 73 mEq per kilogram wet weight. This animal exhibited marked weakness and a constant bigeminal rhythm yet cardiac histologic changes were absent.

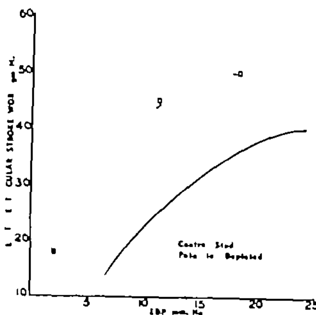


Fig 3 The MSER increased at all levels of LVEDP in this K depleted animal

systemic resistance had a normal skeletal muscle K^+ concentration and the smallest fall in serum K^+. Two control animals also showed an increased MSER and both these animals had a low serum K^+ (3 0 mEq and 3 ? mEq)

Ventricular function curves Stroke work was increased following potassium depletion (Fig 3) and there was also a tendency to increased LVMW. Stroke work was unchanged in the controls but there was also a tendency to increased LVMW (Table II)

Histology No consistent histologic changes were seen in the cardiac muscle of the depleted animals.*

Discussion

Studies of isolated cardiac muscle preparations have shown a stable contractile state with bathing solutions containing from 2 mEq per liter to 10 mEq per liter of potassium. However contractility was augmented when the potassium concentration was reduced below 2 mEq per liter.[1,3] Acute experiments with a heart lung preparation have shown no marked changes in contractility with serum potassium ranging from 2 mEq per liter to 11 mEq per liter.[6] Hemodialysis-induced acute hypokalemia resulted in an increased LV dp/dt and left ventricular contractility in two intact dogs studied by Goodyer.[7]

Moreover interventions which increased cardiac contractility result in an efflux of myocardial potassium, an observation documented during paired stimulation,[8] increased wall tension,[9] and increased contractile rate.[10] It has been speculated that hemodynamically induced increases in myocardial O_2 consumption promote a net loss of potassium which in turn results in the improved contractility.[11] However potassium loss during enhanced contractility should not be used to predict the effect of chronic potassium depletion or the role of potassium in altering the contractile state.

Our studies indicate that moderately severe chronic potassium depletion results in enhanced cardiac performance. The augmentation in MSER, LV dp/dt and LVSW plus the trend toward increased LVMW demonstrate increased contractility. The increased LV dp dt assumes more importance in face of the reduced arterial pressure and heart rate—interventions which normally reduce LV dp/dt.[12] Although acute increases in stroke volume increase LV dp/dt, chronic increases in stroke volume have little effect on LV dp/dt.[12] When the cardiac contractile state is unaltered a reduced heart rate and increased stroke volume will prolong the ejection time and MSER is unchanged or slightly increased. Consequently the increased MSER implies a positive inotropic effect with potassium depletion.

The mechanism of enhanced contractility is not defined but the ratio of intracellular to extracellular potassium (Ki/Ke) is important.[3,4] Acute reductions in potassium concentration of the perfusate increase the Ki/Ke ratio. Chronic depletion in our dogs also increased the Ki/Ke ratio since the extracellular potassium concentration decreased by almost 40 per cent whereas the cardiac muscle potassium fell by less than 10 per cent. The potassium shifts and change in Ki/Ke occurring with chronic depletion may effect contractility only indirectly by the associated changes in intracellular sodium and calcium concentrations. High potassium concentrations, which would decrease the Ki/Ke ratio impaired the function of isolated cardiac muscle

*Kindly reviewed by Dr Mal Kaarson.

21. Smith, S. G., Black-Schaffer, B., and Lasater, T. E.: Potassium deficiency syndrome in the rat and the dog. A description of the muscle changes in the potassium-depleted dog. Arch. Path. (Chicago) 49:185, 1950.
22. Darrow, D. C., and Miller, H. C.: Production of cardiac lesions by repeated injections of desoxycorticosterone acetate. J. Clin. Invest. 21:601, 1942.
23. McAllen, P. M.: Myocardial changes occurring in potassium deficiency. Brit. Heart J. 17:5, 1955.
24. Kaye, J. D.: Death in potassium deficiency. Report of a case including morphologic findings. Circulation 5:766, 1952.
25. Perkins, J. G., Peterson, A. B., and Riley, J. A.: Renal and cardiac lesions in potassium deficiency due to chronic diarrhea. Amer. J. Med. 8:115, 1950.
26. Molnar, Z., Larsen, K., and Spargo, B.: Cardiac changes in potassium-depleted rat. Arch. Path. (Chicago) 74:339, 1962.
27. Nickerson, M., Karr, G. W., and Dresel, P. E.: Pathogenesis of electrolyte-steroid-cardiopathy. Circ. Res. 9:209, 1961.

The functional changes associated with potassium-depletion cardiac necrosis remain unknown

Perhaps there exists a spectrum of cardiovascular effects related to chronic potassium depletion Moderate depletion increases the Ki/Ke ratio which alters repolarization and the appearance of the ECG enhances arrhythmias lowers the maximal sinus node rate reduces arteriolar smooth muscle tone and augments contractility Further potassium loss can then lead to cardiac necrosis and possibly to impaired function

Summary

Chronic potassium depletion in the dog is associated with multiple cardiovascular alterations. The rate of automaticity of the S-A node appears diminished and its response to a chronotropic stimulus is impaired The reduced peripheral resistance causes a decline in the characteristic hyper tensive response to pentobarbital anesthesia Cardiac function is not impaired in the absence of arrhythmias and contractility seems enhanced since potassium depletion produces a significant increase in the mean systolic ejection rate a rise in LV dp/dt and a higher LVSW and a trend to increased LVMW at similar levels of LVEDP These hemodynamic alterations are not associated with light microscopic changes in cardiac muscle

We wish to thank D Phillip Hall for his assistance in performing the Na^+ and K determinations and Dr John Hines for the magnesium analysis.

REFERENCES

1 Hajdu S. Mechanism of staircase and contracture in ventricular muscle, Amer J Physiol. 174:371 1953
2. Cohn K. Pirages S. and Harrison, D C. The effects of potassium on the positive inotropic action of ouabain, Amer Heart J 73:516 1967
3 Nash C. B Davis, F and Woodbury R. A Cardiovascular effects of anesthetic doses of pentobarbital sodium Amer J Physiol 185:107 1956.
4 Seta, K. Hellerstein E. E., and Vitale, J J: Myocardium and plasma electrolytes in dietary magnesium and potassium deficiency in the rat, J Nutr 87:179 1965.
5. Dawson J B and Heaton, F W: The determination of magnesium in biological materials by atomic absorption spectrophotometry Biochem. J 80:99 1961
6. Hochrein H., Zaqqa, Q Pelschallies, B and Wollheim, E Experimental studies on the hemodynamic and myocardial metabolism of electrolytes in hypo and hyperpotassemia and under the influence of digitalis, Acta. Cardiol. (Brux.) 20:148 1965
7 Goodyer A. V M Goodkind M. J and Stanley E. J The effect of abnormal concentrations of the serum electrolytes on left ventricular function in the intact animal Amer. Heart J 73:516 1967
8. Sarnoff S. J., Gilmore, J P Daggett, W M Mansfield P B Weisfeldt M L., and McDonald R. H Myocardial dynamics, contractility O_2 consumption and K^+ balance during paired stimulation, Amer J Physiol. 211:376, 1966.
9 Gilmore, J P and Gerlings, E. D Influence of developed tension on myocardial potassium balance in the dog heart, Circ. Res. 22:69 1968.
10. Langer G. A. and Brady A. J Potassium in dog ventricular muscle Kinetic studies of distribution and effects of varying frequency of contraction and potassium concentrations of perfusate, Circ. Res. 18:164 1966.
11 Sarnoff S. J Gilmore, J P McDonald R. H Daggett W M., Weisfeldt, M L. and Mansfield R. B Relationship between myocardial K balance, O consumption and contractility Amer J Physiol 211:361 1965
12. Wallace, A. G Skinner N S., and Mitchell, J H Hemodynamic determinants of the maximal rate of rise of left ventricular pressure, Amer J Physiol. 205:30 1963
13 Gleason, W L. and Braunwald E. Studies on the first derivative of the ventricular pressure pulse in man, J Clin. Invest. 41:80, 1962.
14 Surawicz, B Chlebus, H and Mazzoleni, A.: Hemodynamic and ECG effects of hyperpotassemia Differences in response to slow and rapid increases in concentration of plasma K, Amer. Heart J 73:647 1967
15 Kaltenbach M Schoppe, W Kaul, A., Koch, K. M and Hierholzer K. La eficiencia del corazon, en condiciones de hipopotasemia, en el hombre Arch. Enferm. Corazon 68:357 1965.
16. Kleiger R. E. Seta K. Vitale, J J and Lown, B Effects of chronic depletion of potassium and magnesium upon the action of acetylstrophanthidin on the heart Amer J Cardiol. 17:520 1966.
17 Lieberman, M Effects of cell density and low K on action potentials of cultured chick heart cells, Circ. Res. 21:879 1968.
18 Gettes, L. and Surawicz, B: Effects of low and high concentrations of potassium on the simultaneous recorded Purkinje and ventricular action potentials of the perfused pig moderator band Circ. Res. 23 717 1968.
19 Friedman, M Freed, S. C and Rosenman, R. H. Effect of potassium administration on (1) peripheral vascular reactivity and (2) blood pressure of the potassium-deficient rat, Circulation 5:415 1962.
20. Bohr D F Brody D C., and Cheu, D H.: Effect of electrolytes on arterial muscle contraction, Circulation 17:746, 1958.

lead systems (1) similarity of different lead systems (2) accuracy of electrical orthogonality including equal representations of all parts of the heart in any VCG lead and (3) anatomic identifiability of the spots for electrode positions and tolerance of the system for slight electrode misplacement as inevitable in clinical application

Investigators agree that the similarity between corrected lead systems is greater than that between any of the corrected lead systems and any uncorrected systems, such as the cube system Langer and associates,[3] Pipberger and Lilienfield[4] and Burger and co-workers[5] concluded, on the basis of their investigations, that the SVEC III the Frank, and the McFee and Parungao[6] systems were quite similar and reasonably interchangeable while Simonson, Schmitt, and associates,[7] Beswick and Jordan and Horan and associates[10] demonstrated measurable differences and therefore lack of complete interchangeability

Regarding electrical orthogonality the conclusions of the various authors (Schmitt,[11] Brody and Arzbaecher [12] Fischmann and Elliott[13,14]) are somewhat at variance because of different criteria used for evaluation i.e. lumped dipole versus distributed dipole. However most observers found SVEC III lead system of superior performance.

All investigators[5, 15] found that the Frank lead system has the poorest tolerance to electrode displacement.

We have been urged on several occasions to develop a compromise electrode system preserving as much as possible the special merits of the SVEC III system but gaining the relative simplicity of corrected lead systems utilizing fewer electrodes. In particular we would like to maintain relative insensitivity to patient posture and exact anatomical electrode positioning with a high degree of accuracy and orthogonality while reducing the number of electrodes needed especially where they must be in awkward locations as, for example, on the patient back. These electrodes are particularly difficult to place accurately when the patient is lying on his back in bed.

In the following study we have examined the possibility of substituting a single suitably placed posterior electrode as a substitute for the four back electrodes of the standard SVEC III system as these are most time consuming and difficult to apply especially when used on acutely ill patients. This study examines a number of compromise locations for a back electrode and attempts to minimize the error defined in terms of the differences of QRS and T potentials between a Z lead obtained with the original standard SVEC III system (i.e., four back electrodes) as against a Z lead obtained with the exploring single back electrode. Beyond this practical purpose results of some theoretical interest in regard to distribution of ECG potentials on the back and the problem of electrical cancellation were obtained

Experimental procedure

To establish a working anatomical location grid for positioning back electrodes the following map of thirty electrode positions was used. A rectangle was marked with corners at the positions of the standard four back electrodes of the SVEC III system. This rectangle was now made into a grid of 25 electrode positions, five vertical columns and five horizontal rows, equally separated with potential electrode positions at each of the grid intersections. Below this rectangle, an additional extrapolated row was added similarly marked off into five positions, thus yielding a total of 30 measurement positions for each subject. The performance of a possible back-electrode position was then examined in terms of the difference between that electrode position potential and the potential of the simultaneously tested standard SVEC III back Z lead comprising a weighted combination of the four corner electrodes. An ideal substitute single electrode would obviously appear to be one somewhere near the center of this rectangle which would, hopefully differ trivially in its potential from the weighted standard combination. In all of the work on normals and abnormals the standard Z lead was recorded simultaneously with the difference potential between the ne

Simplification of the SVEC-III lead system

*Masashi Yokoi, M.D.**
Otto H. Schmitt, Ph.D.
Ernst Simonson, M.D.
Minneapolis, Minn.

The SVEC III lead system developed in 1954[1] represents one of the first major attempts to synthesize on the basis of quantitative torso-model experiments a lead system orthogonalized ("corrected") so as to represent all components of the heart moment equally and to a uniform orthogonal scale with minimal sensitivity to electrode position. As has been amply demonstrated, it is impossible to generate an ideal uniform orthogonal normalized lead system with the use of the theoretical minimum of four electrodes required to generate three potential differences, and it is always possible to improve any given lead system somewhat by adding yet another electrode. A corrected orthogonal electrode system designed for clinical application is therefore a weighted choice between grossly inadequate representation with the use of too few electrodes, and an unnecessary complication and inconvenience to the patient from the use of too many electrodes. It is obviously possible to make bad lead systems with the use of many electrodes, but it will surely be necessary to use more than four to generate a good approximation to an orthogonal lead system.

By means of the fourteen electrodes of the SVEC III lead system good approximation to electrical orthogonality was achieved, and still within reasonable limits of easy clinical application.

After introduction of the SVEC III lead system, several other corrected lead systems with fewer electrode positions were proposed. Of course, reduction of electrodes will reduce the time for taking the vectorcardiograms (VCG). With the increasing volume of clinical vectorcardiography, the saving of time is important, since putting on the electrodes takes as much, if not more, time than obtaining the records. Obviously, that lead system which combines reasonably good electrical orthogonality with the minimum number of electrode positions would be the choice for clinical application. Apparently a majority of clinical vectorcardiographers believe that the Frank[2] lead system meets this demand, since the Frank lead system is, at present, more widely used than any other corrected lead system.

Numerous comparisons have been made between the various proposed VCG systems. There are several major criteria for superiority (or inferiority) of the various

From the Biophysics Group, University of Minnesota and Mt. Sinai Hospital, Minneapolis, Minn.

Supported by Grants HE-11325, HE-00313, and HE-07375 of the National Heart Institute of the United States Public Health Service.

Reprint requests to: Dr. Otto H. Schmitt, Professor of Biophysics-Bioengineering, Department of Electrical Engineering, University of Minnesota, Minneapolis, Minn. 55455.
*Department of Medicine, Nagoya University, Japan.

Table 1 Mean amplitude difference and range of differences between standard and simplified SVEC III Z lead

	A		B		C		D		E	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
*Thirty back electrode positions—ten normal subjects**										
1 QRS	0.26	0.13-0.46	0.18	0.04-0.37	0.24	0.11-0.48	0.33	0.15-0.54	0.44	0.25-0.75
T	0.08	0.01-0.14	**0.01**	0.00-0.08	0.10	0.01-0.20	0.12	0.06-0.20	0.15	0.07-0.23
2 QRS	0.23	0.12-0.42	**0.16**	0.04-0.11	0.26	0.11-0.39	0.35	0.23-0.53	0.45	0.26-0.85
T	0.07	0.01-0.16	0.01	0.00-0.08	0.10	0.06-0.13	0.13	0.08-0.24	0.16	0.09-0.32
3 QRS	0.36	0.31-0.76	0.33	0.14-0.57	0.17	0.09-0.31	0.21	0.13-0.40	0.31	0.16-0.42
T	0.17	0.09-0.30	0.08	0.02-0.16	**0.03**	0.00-0.08	0.07	0.00-0.15	0.11	0.05-0.17
4 QRS	0.32	0.22-0.83	0.12	0.08-0.17	**0.1**	0.03-0.28	0.24	0.15-0.42	0.34	0.18-0.49
T	0.11	0.07-0.27	0.06	0.00-0.13	0.05	0.00-0.09	0.10	0.01-0.15	0.12	0.06-0.19
5 QRS	0.55	0.19-0.82	0.45	0.10-0.75	0.20	0.01-0.41	0.17	0.05-0.47	0.29	0.15-0.45
T	0.17	0.07-0.33	0.15	0.05-0.28	0.05	0.00-0.15	**0.04**	0.00-0.13	0.07	0.01-0.14
6 QRS	0.56	0.22-1.11	0.38	0.15-0.76	0.18	0.06-0.34	0.19	0.10-0.40	0.25	0.01-0.43
T	0.16	0.10-0.29	0.10	0.03-0.18	**0.01**	0.00-0.07	0.06	0.00-0.14	0.07	0.01-0.16
Thirty electrode positions—ten representative abnormal subjects										
1 QRS	0.32	0.18-0.40	0.27	0.14-0.40	0.25	0.10-0.40	0.27	0.11-0.47	0.30	0.16-0.46
T	0.09	0.01-0.10	0.08	0.01-0.09	**0.03**	0.01-0.10	0.08	0.02-0.13	0.08	0.03-0.13
2 QRS	0.33	0.12-0.60	0.24	0.05-0.51	0.23	0.06-0.50	0.27	0.15-0.44	0.30	0.09-0.40
T	0.10	0.02-0.14	**0.05**	0.01-0.15	0.07	0.02-0.11	0.09	0.02-0.12	0.09	0.02-0.13
3 QRS	0.35	0.23-0.66	0.23	0.09-0.50	0.14	0.06-0.22	0.22	0.09-0.39	0.28	0.16-0.45
T	0.09	0.02-0.13	**0.05**	0.02-0.08	**0.03**	0.01-0.05	**0.03**	0.02-0.08	0.07	0.02-0.09
4 QRS	0.36	0.19-0.57	0.33	0.09-0.42	0.14	0.05-0.19	0.19	0.09-0.26	0.21	0.16-0.33
T	0.08	0.02-0.10	**0.03**	0.01-0.07	**0.04**	0.01-0.07	**0.03**	0.02-0.06	0.08	0.01-0.11
5 QRS	0.38	0.15-0.69	0.31	0.07-0.52	0.27	0.07-0.53	0.26	0.13-0.53	0.31	0.15-0.60
T	0.11	0.03-0.23	0.08	0.00-0.15	0.09	0.02-0.13	0.08	0.03-0.11	0.10	0.01-0.13
6 QRS	0.49	0.23-0.81	0.32	0.16-0.48	0.27	0.12-0.43	0.31	0.09-0.36	0.33	0.18-0.57
T	0.13	0.03-0.26	0.12	0.02-0.19	0.11	0.03-0.16	0.11	0.02-0.18	0.12	0.01-0.17

* A rectangular grid of uniformly spaced back electrode positions, arranged in six rows and five columns as shown in the table, was tested individually by comparison with the standard SVEC III Z lead. Differences for the same beat for the standard SVEC III lead and the test position under examination referred to the standard SVEC III [illegible] were recorded for each position for each individual. [illegible] the group mean peak-to-peak [illegible] for the QRS and T along with the extreme individual values in each group, each individual measurement being based on the mean of [illegible] heartbeats; thus, the first series of entries [illegible] in the table indicates that the mean peak-to-peak QRS [illegible] for ten normal subjects was [illegible] the least for the group, 0.13, and the largest, 0.44, for the QRS complex. The second portion of the table contrasts the corresponding values for a group of ten abnormals representing [illegible] of typical disease abnormalities. In each group the entries representing the lowest value of the mean difference for the QRS and T respectively are set in bold face type. [illegible] representing the regular array of four electrodes, [illegible] electrode positions are near the center of the array and tend to lie along an upper left to lower right diagonal about the center

simplified back electrode and the standard combined back electrode to provide an error voltage measurement In a third channel of the recording system the new or simplified Z lead was also recorded between the standard weighted combination chest connection and the simplified single electrode back position By comparing this Z lead with the standard SVEC Z lead it is possible by visual inspection to determine whether an obvious difference exists on the displayed or plotted-out record

It is important to point out that it becomes increasingly evident from recent work that the contributing electrode to a compound lead may be causing much greater error through high-contact impedance than from the much studied lack of anatomical ideal location In these studies therefore we have in every case used a very high impedance individual buffer amplifier on any electrode being recorded so that in effect its impedance became a trivial error in the recording All weighted combinations are generated after buffer amplification A fail safe light indicator system was in constant operation so that appearance of large impedance in any electrode immediately warned the operator to discontinue the experiment and improve lead contact In the earlier phases of the experimentation standard small suction-cup electrodes of nickel silver were utilized with well rubbed in and localized electrode paste but with growing concern about electrode position impedance and paste spread nonpolarizable silver–silver-chloride electrodes fastened by adhesive to the skin were substituted In this limited study it was thought important to have at least a minimal sample of clinically healthy subjects and a sample population of representative abnormal subjects. For the normal subjects, ten young healthy men with no present or past pathological history aged 19 to 40 years with a mean of 26 5 years were used Because considerable manipulation of back electrodes was essential the experiments were done with the subject lying prone in a comfortable position and moving as little as possible during the series of electrode manipulations. Because the SVEC III electrode placement is based on anatomical landmarks and symmetry the actual electrode spacing varies with the subject's dimensions so that in the ten normal subjects the electrode separation in the rectangular grid ranged over a ratio of approximately 3 2 4 5-3 0 cm with a mean of 3 8 in the horizontal direction and 3 5-2 5 cm with a mean of 3 0 cm. in the vertical direction. Considerable care was taken to avoid casual smearing of paste or other interference between electrodes in the different positions, as recent experience has shown that paste in the vicinity of surface electrodes when skin abrasion is limited may cause equivalent shifting of the electrode position. Results were analyzed by transcribing the FM magnetic tape records from the 7 channel IRIG format tape record onto precision Brush ink writer records or alternatively records were read by a new cursor program directly on the screen of a computer display In this display a two-second segment of the record is displayed stationary or moving forward or backward at a chosen rate A cursor dot, like the cross hair on the cursor of a slide rule identifies corresponding times on the several vector component traces and measures chosen points automatically For each lead configuration on a subject enough record was made that analysis could in general be based on the average of five consecutive beats. In fact, at least 20 seconds of record was made available in each case.

Results

Preliminary examination of experimental results showed that it was impossible to regard the back-electrode choice as a trivial one Many experimenters believe that the cardiographic variation across the back is relatively small so that the rear electrode position is unimportant but this is clearly not the case It became immediately obvious that there is no easy choice of a substitute single electrode As one examines the records, one sees that the conclusions are going to depend very heavily on the statistical functions used to interpret the discrepancies.

It is clear that the differences in diagnostic interpretations are not going to be

particular sample-electrode locus divided by the mean for that individual We can compare the error voltages, defined as the peak to-peak QRS amplitude of the error or the correspond ng values for the T wave. These are taken as separate considerations and do, indeed, separate in recommending a best compromise electrode location.

As one estimator we can compare the error oltage of an indi idual to his own Z-lead voltage and form a combination of these fractional-error voltages. Alternatively we can compare the mean of individual-error voltages to the mean of the several total Z voltages. We have chosen to show both RMS and simple *mean ratios*, the root mean square being used to emphasize individual severe aberrations, which we feel represent greater hazard to misinterpretation than do many small errors. Shown separately are the weighted errors for the normal and for the abnormal subjects as well as for the lumped population

It is clearly evident from examination of the potential distributions in Tables I and II that minimal error is found near the center of the square being represented. This is hardly surprising It is, however significant that the band of minimal error extends on a diagonal from approximately upper left to lower right, and that deviation from the midpoint in these directions is much less likely to cause error than a corresponding orthogonal displacement. Our conclusion, then is that a single electrode, *if it is to be used, may well be* placed at the center of the rectangle or perhaps a l ttle above and to the left of the center Small errors in this choice are not very significant in terms of the errors already present due to substituting the single electrode. In estimating the penalty for this simplification we see that errors in the range of 10 per cent are to be expected and that a small percentage will have magn tude errors of the order of 25 per cent or even more. On the whole, however examination of typical records does not show extreme difference between SVEC III and this simplified version

The difference including time and shape differences, is illustrated by the error vector pattern of Fig 1 Here the standard SVEC III left sagittal vector loop is shown utilizing the simplified Z lead There is also shown in the third column the difference loop between the first two plotted to the same scale. Any vertical residue here represents error It can be seen that the shapes of the loops are quite similar and would be interpreted the same clinically even though some appreciable error voltage exists. It is noteworthy that the error voltage is not systematically increased in abnormals as might have been expected so that the simplified lead is not less accurate for abnormal than for normal subjects.

An over all conclusion might be that *this simplified SVEC III system, with the* use of one electrode near the center of the normal rectangle of back electrodes, is a workable substitute, better than most corrected lead systems, but noticeably short in performance of the actual SVEC III system. In our opinion, it would be an acceptable substitute in a situation where the penalty for the use of a full array of electrodes is severe and where precision measurements or crucial determinations are not dependent on the results.

Summary

An effort was made to develop a simplification of the SVEC III lead system which would preserve most of its accuracy and immunity to exact electrode-positioning requirements while reducing the number of electrodes in the awkward back positions. A rectangular grid of 30 uniformly spaced back-electrode positions, including the four original SVEC III Z-lead positions, was tested position by position in comparison with the standard SVEC III Z lead n ten healthy men and ten patients with different types of cardiac pathology Potential differences between the single exploring Z electrode and the standard combined weighted Z lead were recorded and statistically evaluated as absolute differences, relative differences in respect to peak to-peak amplitude, and root mean squares. The smallest errors occurred near the center of the rectangle, in an oblique line from upper left to lower right, without appreciable differences between the normal subjects and the patients. The typical error for good electrode positions was in

Table II RMS potential difference between simplified and standard SVEC III Z-lead expressed in millivolts and in percentage of total Z lead potential

	A		B		C		D		E	
	Mv	%	Mv	%	Mv	%	Mv	%	Mv	%
Thirty back electrode positions—ten normal subjects										
1 QRS	0 28	21 1	0 20	14 9	0.27	20 2	0.35	26 4	0 47	34.9
T	0 09	34 0	0 01†	13.8	0 11	39.2	0.13	47.5	0.16	58.1
2 QRS	0.27	20 4	0 18	13.8	0 28	20 8	0.36	27.2	0.49	36 5
T	0 08	30 4	0 05	19 8	0 10	37.3	0 12	42 7	0.18	65.7
3 QRS	0.58	43 8	0.37	28 1	0 18	14 0	0 23	17 4	0.33	24 9
T	0 19	69 0	0 09	34.3	0 04	13.3	0.09	31 6	0.12	42 6
4 QRS	0.56	41 8	0.34	25.5	0 19	14 4	0.26	19.3	0.35	26.1
T	0 16	59 0	0 07	25.5	0 06	20 6	0 11	39.5	0 12	45.9
5 QTS	0.58	43.8	0.49	36 8	0.23	17 6	0.20	15 4	0.30	22.4
R	0 19	70.0	0 17	61.3	0 07	27 0	0.05	19 6	0 03	29 9
6 QRS	0 62	46.6	0 42	31 6	0 20	14.8	0 21	16.1	0.27	20.5
T	0 18	61 9	0 11	40 7	0 04	13 8	0 07	26.2	0 08	30.1
Thirty electrode positions—ten representative abnormal subjects										
1 QRS	0.33	12.3	0.28	10.5	0.26	9 7	0.29	10.8	0.32	11 7
T	0.13	18.6	0 11	16 1	0.10	14.8	0.10	14 4	0.09	12.4
2 QRS	0.37	13.5	0.29	10 7	0.26	9 7	0.28	10 4	0.32	11.8
T	0 15	20 8	0 10	14 8	0.09	12 0	0 10	13 4	0 10	13 4
3 QRS	0.37	13 5	0.25	9 4	0 15	5.7	0.24	8.7	0.29	10.8
T	0 11	14 9	0 07	9.2	0 04	5.3	0 06	7 9	0 08	10.9
4 QRS	0 38	14.2	0 24	8 9	0 13	3.7	0.20	7.2	0 25	9.2
T	0 09	12 8	0 06	9 1	0 06	8.3	0.06	9 1	0.09	12.1
5 QRS	0 41	15 2	0.33	12 4	0.30	11.3	0.29	10 6	0.34	12.7
T	0 14	20 4	0 11	15 6	0 10	13.6	0 09	12 1	0.12	16.4
6 QRS	0.52	19 4	0 33	12.2	0.29	10 8	0.26	9.5	0.36	13.3
T	0 18	24 8	0 15	21 4	0.15	20 9	0.14	20.0	0 15	21.2

*This table represents the same group of ten normal and ten abnormal subjects covered by T ble I but evaluated here in terms of root mean square value for each group of ten and the percentage of the total Z-lead potential represented by the residual error oltages. It will be noted that while the error potential for the best locations is small in millivolts, it may be significant in percentage of total potential. The apparent anomaly of higher percentage error voltages in normal than in abnormal subjects for the best compromise positions probably arises mainly from the fact that the bnormal subjects generate larger QRS and T oltages than normal individuals, so that minor perturbations can cause relatively large percentage error

†In each group the entries representing the lowest alue of the mean difference for the QRS and T respecti ely are set in boldface type as best choices for single electrode position representing the regular array of fou electrodes.

directly proportional to any simple measure of the electrical potential difference be tween one lead system and another Certainly one will expect that a large difference in amplitude between one lead system and another interpreted in any given fashion will lead to larger interpretive differences yet it is also obvious that a lesser change in amplitude difference accompanying a significant change in wave form in a way related to diagnostically sensitive features may be more important. Thus it becomes evident that the way of scoring error voltages can grossly alter the conclusions found

It is on this basis that we have provided several alternative evaluations following the general principle that a large potential difference suggests a large error in interpretation and offering alternative choices of combinatorial statistics for each of which rationalizations can be found

Three basically different statistical representations are used to show the relative importance and size of error as a function of the positioning of the single representative probe as a substitute for the normal SVEC III weighted combination of four probes. The several different tabular values are presented to form a combined estimate of errors. First we can consider the ratio of error voltage for an individual at a

6. McFee, R., and Parungao, A. An orthogonal lead system for clinical electrocardiography Amer. Heart J 62:93, 1961
7. Simonson, E., Nakagawa, K., and Schmitt, O. H. Respiratory changes of the spatial vectorcardiogram recorded with different lead systems, Amer. Heart J 54:919 1957
8. Simonson, E., Schmitt, O. H., and Nakagawa, K. Quantitative comparison of eight vectorcardiographic lead systems, Circ. Res. 7:296, 1959.
9. Berwick, F W and Jordan, R. C. Quantitative comparison of six nominally orthogonal vectorcardiographic systems, Amer. Heart J 67:657 1964.
10. Horan, L. G., Flowers, N C., and Brody D A. The interchangeability of vectorcardiographic systems, Amer. Heart J 70:365 1965
11. Schmitt, O H. Lead vectors and transfer impedance, the electrophysiology of the heart, Ann. N Y Acad. Sci. 65 1092, 1957
12. Brody D L, and Arzbaecher R. C.: A comparative analysis of several corrected vectorcardiographic leads, Circulation 29:533 1964
13. Fischmann, E. J and Elliott, B. J: Experimental comparison of "parallel grid leads" with simple bipolars and the SVEC III Frank, and McFee-Parungao systems. I. Sagittal leads, Amer. Heart J 67:792, 1964.
14. Fischmann, E. J and Elliott B. J Experimental comparison of parallel grid leads with simple bipolar and the SVEC III Frank, and McFee-Parungao systems. II Transverse and vertical leads, Amer. Heart J 70:627 1965.
15. Simonson, E., Horibe, H. Okamoto, N and Schmitt, O H.: Effect of electrode displacement on orthogonal leads, *in* Vectorcardiography—1965 Symposium held at the Long Island Jewish Hospital, N Y Amsterdam, 1966, North-Holland Publishing Company

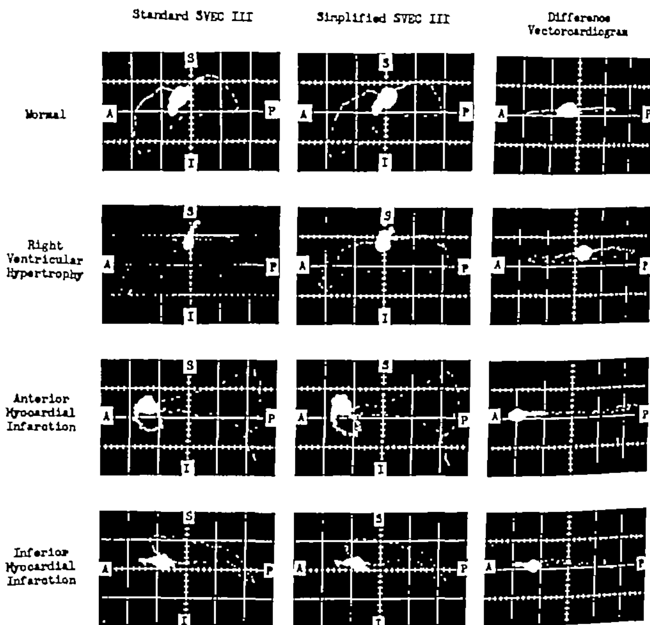


Fig 1 Left sagittal-vector loops taken with standard and simplified SVEC III system on a normal subject and on three cardiac patients. Last column shows the error vector loop produced by plotting the difference between standard and simplified SVEC Z leads (vertically) against the usual Z lead (horizontally) This error loop is plotted to the same voltage scale as the other loops.

the range of 6 to 15 per cent, which is not negligible but as shown in illustrations would not affect the clinical interpretation appreciably It is concluded that the simplified SVEC III system is workable for clinical routine interpretation probably better than some other corrected lead systems, but not quite as accurate as the original SVEC III system

REFERENCES

1 Schmitt, O H and Simonson, E. The present status of vectorcardiography Arch. Intern. Med 96:574, 1955.

2 Frank E. An accurate clinically practical system for spatial vectorcardiography Circulation 13 737 1956.

3 Langner P H Okada, R. H Moore, S. R., and Fies, H L. Comparison of four orthogonal systems of vectorcardiography Circulation 17 46 1958.

4 Pipberger H. V and Lilienfield, L. S. Application of correct electrocardiographic lead systems in man, Amer J Med 25:539 1958.

5 Burger H C von Brummelen, A. G and van Herpen G. Compromise in vectorcardiography II Alternations of coefficients as a mean of adapting one lead system to another—subjective and mathematical comparison of four systems of VCG, Amer. Heart J 61:666, 1962.

Close bipolar electrodes were made by threading two Teflon-coated steel wires (0.005 inch in diameter) into a 22 gauge needle. The wires were bent back over the point of the needle and cut 1 mm from the tip. This resulted in two small hooks which were insulated except at the very tip. When the needle was inserted into the myocardium and withdrawn the two electrodes remained in the tissues in close proximity to each other. These electrodes were implanted (1) into the sinus node (SN) near the junction of the superior vena cava with the right atrium (2) in the region of Bachmann's bundle (BB) approximately 5 mm. from its junction with the sinus node (3) into the tips of the right atrial appendage (RAA) and left atrial appendage (LAA) (4) into the posterior portion of the left atrium (LAP) in the area of its junction with the inferior pulmonary veins and (5) in the proximal portion of the coronary sinus (CS) approximately 8 to 10 mm. from its mouth. A standard Lead II ECG and a His bundle electrogram (HBE) were simultaneously recorded with the atrial electrograms on a multichannel oscilloscopic photographic recorder (Electronics for Medicine) at paper speeds of 100 or 200 mm per second. The His bundle electrogram was obtained by inserting an above-described bipolar electrode into the region of the bundle of His using the technique of Scherlag and associates. Another such electrode was inserted into the free wall of the right ventricle and used for ventricular pacing studies. All bipolar electrograms were obtained with filter frequencies set at 40 to 500 c.p.s. The recording bipolar electrodes were also used to pace the heart, using a battery powered pacemaker (model 5837 R wave-coupled pulse generator Medtronic, Inc.) which delivered impulses of 2 msec. duration at approximately twice threshold.

A bipolar wire electrode was also inserted into the peripheral cut end of the isolated right cervical vagus nerve. The nerve was stimulated by means of the Grass stimulator (model S8) delivering 6 to 10 v rectangular impulses of 2 msec. duration at a frequency of 40 per second. In 18 experiments the sinus node was ablated by crushing it with a surgical clamp, or by injecting 40 per cent formaldehyde along the whole length of the sinus node with a 25 gauge needle or by both.

Results

In the initial stages of each experiment all animals were in normal sinus rhythm. The sequence of atrial activation during this rhythm as determined by the multiple bipolar electrogram recordings, was as follows SN BB RAA, LAA, LAP and CS. Occasionally minor variations were observed in the sequence of the left atrial electrograms, with the LAP occurring simultaneously with or before LAA. These variations probably reflect either physiologic variations of intra-atrial conduction or minor variations in the exact positioning of the electrodes from one experiment to the other. In all cases the sinus beats exhibited upright P waves in the surface Lead II.

In 18 dogs ectopic right atrial beats and rhythms were observed (Figs. 1 to 7). In these beats the sequence of activation had differed from that seen in normal sinus rhythm with the earliest electrical activity recorded by the RAA electrode followed sequentially by SN BB LAA, LAP and CS. An ectopic right atrial rhythm was defined as three or more successive beats having the above-described altered sequence of activation.

While the normal rate in dogs under our experimental conditions, was approximately 150 to 180 beats per minute, the rates of discharge of the ectopic right atrial foci varied considerably. Single ectopic beats, either conducted to the ventricles (Fig. 5) or blocked above the bundle of His, presumably at the level of the A V node were very frequent (Fig. 2). The rate of the ectopic right atrial rhythms ranged between 100 and 300 beats per minute. The duration of these rhythms ranged between a few seconds and three minutes. Rhythms of higher rates were also observed but will not be considered in this report.

Ectopic right atrial beats were observed during vagal stimulation, following destruction of the sinus node, during ventricular pacing and occurring spontaneously.

Spontaneous ectopic right atrial beats

Ectopic right atrial rhythms Experimental and clinical data

*M Mirowski M D**
S H Lau M D
Andrew L Wit Ph.D
Charles Steiner M D
Gustavus A Bobb B Sc
*Bernard Tabatznik M.D**
Anthony N Damato M.D
Staten Island N Y and Baltimore Md

The nature of pacemaker activity in locations other than the sinus node has been the subject of much interest Recently the existence of ectopic right atrial rhythms was suggested by vectorial analysis of clinical electrocardiograms (ECG s) characterized by normal P wave configuration in the extremity leads and by P wave inversion in the precordial leads from V_1 to V_4.[1]

In order to test the concept that ectopic right atrial automaticity exists, a series of experiments was performed In addition clinical ECG s which met the above criteria for ectopic right atrial rhythms were studied The purpose of this communication is to correlate and report these experimental and clinical observations.

In this article the term ectopic right atrial rhythms will refer to rhythms originating in the right atrium outside the sinus node and the atrioventricular junctional area

Experimental data

Methods Experiments were performed on 25 mongrel dogs weighing between 15 and 25 kilograms. The method employed was similar to that used in previous studies.[2,3] The dogs were anesthetized with sodium pentobarbital 30 mg per kilogram intravenously additional doses of 10 mg per kilogram being added throughout the study as required A tracheotomy was performed and the respiration was artificially controlled with a Harvard respirator The animals were placed on their left side a right thoracotomy at the level of the fourth interspace was performed the pericardium was incised and the heart was exposed

From the Cardiopulmonary Laboratory United States Public Health Service Hospital, Staten Island, N Y

This work was supported in part by the Federal Health Programs Service, United States Public Health Service Project Py 70-1, National Institutes of Health Projects HE 11829 HE 12536, General Research Support Grant 5SO-1FR-05478-06, and National Aeronautic and Space Administration Contract T 22416.

Received for publication July 20, 1970.

Reprint requests to: M. Mirowski, M.D., Sinai Hospital of Baltimore, Baltimore Md. 21215.

*Department of Medicine, Sinai Hospital of Baltimore, Inc., Baltimore, Md., and Departments of Pediatrics and Medicine, respectively Johns Hopkins University School of Medicine, Baltimore, Md.

May 1971 Vol. 81 No. 5 pp. 666-676

Close bipolar electrodes were made by threading two Teflon-coated steel wires (0.005 inch in diameter) into a 22 gauge needle. The wires were bent back over the point of the needle and cut 2 mm from the tip. This resulted in two small hooks which were insulated except at the very tip. When the needle was inserted into the myocardium and withdrawn the two electrodes remained in the tissues in close proximity to each other. These electrodes were implanted (1) into the sinus node (SN) near the junction of the superior vena cava with the right atrium (2) in the region of Bachmann's bundle (BB) approximately 5 mm. from its junction with the sinus node (3) into the tips of the right atrial appendage (RAA) and left atrial appendage (LAA) (4) into the posterior portion of the left atrium (LAP) in the area of its junction with the inferior pulmonary veins and (5) in the proximal portion of the coronary sinus (CS) approximately 8 to 10 mm from its mouth. A standard Lead II ECG and a His bundle electrogram (HBE) were simultaneously recorded with the atrial electrograms on a multichannel oscilloscopic photographic recorder (Electronics for Medicine) at paper speeds of 100 or 200 mm. per second. The His bundle electrogram was obtained by inserting an above-described bipolar electrode into the region of the bundle of His using the technique of Scherlag and associates. Another such electrode was inserted into the free wall of the right ventricle and used for ventricular pacing studies. All bipolar electrograms were obtained with filter frequencies set at 40 to 500 c.p.s. The recording bipolar electrodes were also used to pace the heart, using a battery powered pacemaker (model 5837 R wave-coupled pulse generator Medtronic Inc.) which delivered impulses of 2 msec. duration at approximately twice threshold.

A bipolar wire electrode was also inserted into the peripheral cut end of the isolated right cervical vagus nerve. The nerve was stimulated by means of the Grass stimulator (model S8) delivering 6 to 10 v rectangular impulses of 2 msec. duration at a frequency of 40 per second. In 18 experiments the sinus node was ablated by crushing it with a surgical clamp or by injecting 40 per cent formaldehyde along the whole length of the sinus node with a 25 gauge needle or by both.

Results

In the initial stages of each experiment all animals were in normal sinus rhythm. The sequence of atrial activation during this rhythm, as determined by the multiple bipolar electrogram recordings, was as follows: SN, BB, RAA, LAA, LAP and CS. Occasionally minor variations were observed in the sequence of the left atrial electrograms, with the LAP occurring simultaneously with or before LAA. These variations probably reflect either physiologic variations of intra-atrial conduction or minor variations in the exact positioning of the electrodes from one experiment to the other. In all cases the sinus beats exhibited upright P waves in the surface Lead II.

In 18 dogs ectopic right atrial beats and rhythms were observed (Figs. 1 to 7). In these beats the sequence of activation had differed from that seen in normal sinus rhythm with the earliest electrical activity recorded by the RAA electrode followed sequentially by SN, BB, LAA, LAP and CS. An ectopic right atrial rhythm was defined as three or more successive beats having the above-described altered sequence of activation.

While the normal rate in dogs, under our experimental conditions, was approximately 150 to 180 beats per minute, the rates of discharge of the ectopic right atrial foci varied considerably. Single ectopic beats, either conducted to the ventricles (Fig. 5) or blocked above the bundle of His, presumably at the level of the A-V node, were very frequent (Fig. 2). The rate of the ectopic right atrial rhythms ranged between 100 and 300 beats per minute. The duration of these rhythms ranged between a few seconds and three minutes. Rhythms of higher rates were also observed but will not be considered in this report.

Ectopic right atrial beats were observed during vagal stimulation following destruction of the sinus node, during ventricular pacing, and occurring spontaneously.

Spontaneous ectopic right atrial beats

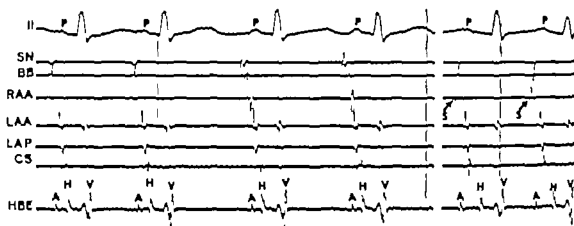


Fig 1 Left panel Conversion of spontaneous ectopic right atrial rhythm (first two beats) to normal sinus rhythm (last two beats) Note the differences in the sequence of activation between the right atrial beats (RAA, BB SN LAA, LAP CS) and sinus beats (SN BB RAA LAA LAP CS) Right panel: stimulation through the recording RAA electrode (see arrows) reproduces the sequence and configuration of the spontaneous ectopic right atrial beats. The increase in the A H interval during stimulated right atrial ectopic beats as compared to the spontaneous ectopic beats is probably due to changes in autonomic tone. The time interval between the vertical lines is 1 000 msec. Key to abbreviations used in this and in the following figures *SN* sinus node *BB* Bachmann's bundle *RAA* right atrial appendage *LAP* posteroinferior portion of the left atrium *LAA* left atrial appendage *CS* inferior portion of the left atrium corresponding to the proximal end of the coronary sinus *LAR* left atrial rhythm *RAR*, ectopic right atrial rhythm *C* control recording. *A* represents atrial depolarization, *H* represents His bundle potentials, and *V* represents ventricular depolarization as reflected in the His bundle electrogram (*HBE*)

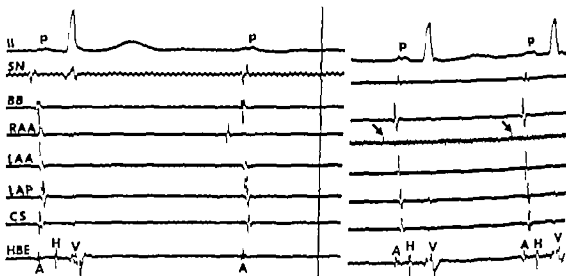


Fig 2 Left panel The first beat is a sinus beat normally conducted to the ventricles. The second beat is an ectopic right atrial beat elicited during vagal stimulation The *RAA* electrogram records the earliest electrical activity This beat is blocked above the bundle of His, presumably at the level of the atrioventricular node. Right panel: Stimulation of the atria through the recording *RAA* electrode reproduces the sequence of activation observed in the unpaced ectopic beat. The arrows indicate the stimulus artefacts.

and rhythms were recorded in six out of 18 studies. These spontaneous rhythms were never observed at the early stages of the experiment but only after the chest was open for an hour or two (Figs. 1 and 7) Also demonstrated in these figures is the usual mode of conversion of the ectopic right atrial rhythm to sinus rhythm

Vagal stimulation was very effective in eliciting right atrial ectopic activity this was observed in 16 out of the 18 experiments. The beats observed were usually single or in short salvos (Fig 2)

After the sinus node was destroyed the pacemaker shifted to automatic centers located either in the right or in the left

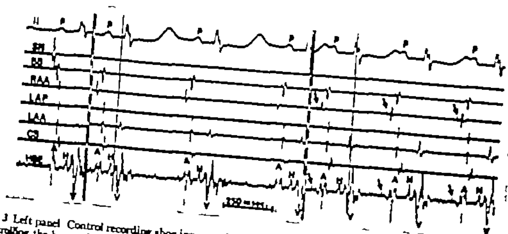


Fig. 3 Left panel Control recording showing sinus beat Middle panel spontaneous ectopic right atrial rhythm controlling the heart after the destruction of the sinus node Right panel Pacing through the recordi g *RAA* electrode reproduces the sequence of activation seen in the ectopic right atrial beats. The arrow indicate the stimulus artefacts.

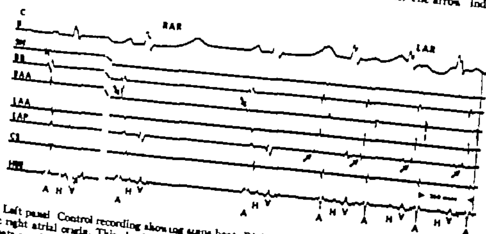


Fig 4 Left panel Control recording showing sinus beat. Right panel The first two beats (open arrow) are of ectopic right atrial origin. This rhythm spontaneously converts to more rapid left atrial hythm, of hich four beats are show (black arrow) Note the differences in sequence and configuration of the electrograms in the three types of beats (sinus, ectopic right atrial, ectopic left trial) The sinus node is destroyed.

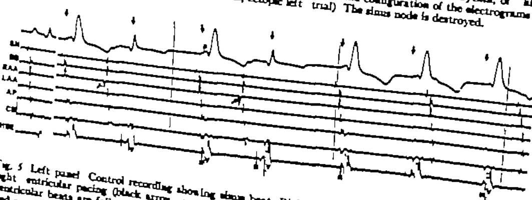


Fig. 5 Left panel Control recording showing sinus beat Right panel Atrioventricular dissociation during right entricular pacing (black arrow correspond to the stimulus artefact) The first and the second paced ventricular beats are followed by ectopic right atrial beats (open arrow) hich are antegradely conducted and capture the ventricles. Consequently the second and fourth pacing stimuli encounter the ventricles in the refractory period and are ineffective. Note that the coupling interval of the ectopic right atrial beats is constant. The ventricular paced beats show retrograde His bundle potentials. The H potential occurs after the stimulus arrow) and after the onset of ventricular depolarisation. The interval bet een the vertical lines is 1 000 msec.

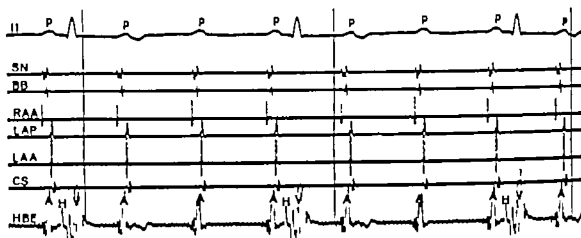


Fig. 6 Advanced 3/1 A V block. The atria are driven by an ectopic right atrial pacemaker (the RAA electrogram record the earliest electrical activity) The interval between the vertical lines is 1 000 msec.

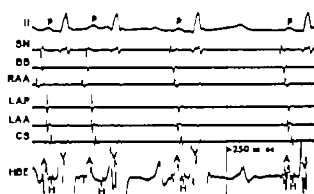


Fig 7 Conversion of an ectopic right atrial tachycardia of 300 beats per minute (first two beats) to a slow sinus rhythm of 120 beats per minute (last two beats)

atrium or in the bundle of His, as judged by alterations in the sequence of activation at the recording electrode sites. Right atrial rhythms elicited by this procedure were relatively stable (Figs. 3 and 4) although conversion to other atrial rhythms occurred An example of a spontaneous conversion from an ectopic right atrial rhythm to a left atrial rhythm is shown in Fig 4

In four experiments ectopic right atrial beats were observed during right ventricular pacing An example of this phenomenon is shown in Fig 5

An interesting example of an ectopic right atrial pacemaker driving the atria during advanced A V block is shown in Fig 6 The block resulted from the interruption of A V conduction during repeated attempts to insert the plunge electrode into the bundle of His. In the absence of multiple atrial electrograms this ectopic activity would not be recognized as such and the atrial rhythm would be assumed to arise from the sinus node.

Atrial pacing through the recording RAA electrode produced beats with the same sequence of activation at the recording sites as that observed in the ectopic right atrial beats (Figs 1 to 3) Marked similarity between the configuration of electrograms of paced and unpaced ectopic right atrial beats was frequently observed

In all instances of ectopic right atrial activity the P waves in the control Lead II were upright although clearly different in shape from the corresponding upright sinus P waves.

Clinical data

Clinical ECG s demonstrating what has been suggested to be ectopic right atrial rhythms, i e tracings characterized by normal P waves in the extremity leads and inverted P waves in the precordial leads from V_1 to V_4[1] were found in 19 patients (17 male and two female) ranging in age from 13 to 78 years with a mean age of 54 years. Twelve patients had coronary artery disease five with acute myocardial infarction Two patients had rheumatic heart disease three had clinically normal cardiovascular systems, and in two cases clinical information was not available Five patients were receiving digitalis glycosides, but only one was suspected of having digitalis toxicity Representative tracings are reproduced in Figs. 8 to 12

The reasons for suggesting that these

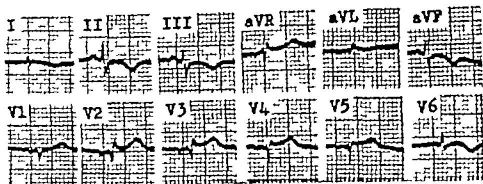


Fig. 8 Ectopic right trial rhythm ECG initially interpreted as showing sinus rhythm. Note P wave configuration in the extremity leads and P ve inversion in the precordial leads from V to V Compare with Fig. 9.

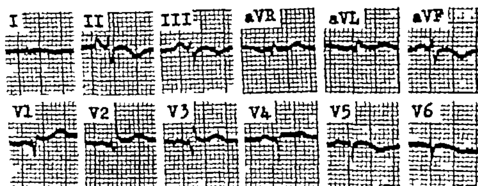


Fig. 9 ECG of the same patient as in Fig. 8, exhibiting sinus rhythm (48 hours later) Note upright P wa es over all the precordial leads

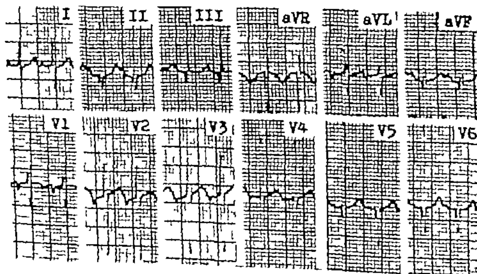


Fig. 10 Ectopic right atrial tachycardia in 13-year-old boy Note inverted P aves in Leads V to V_6. The initial diagnosis was that of sinus tachycardia. Compare ith Figs. 11 and 12.

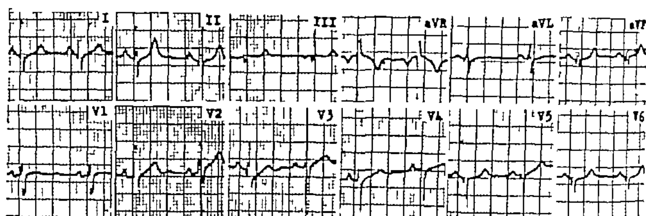


Fig 11 Normal sinus rhythm of the patient whose tracing is reproduced in Fig 10. Note upright P waves in all the precordial leads.

Fig 12 Routine 12 lead ECG showing in each lead conversion of ectopic right atrial tachycardia (first two beats) to normal sinus rhythm (third beat) The conversion was induced by ocular pressure. Note the differences in P wave configuration and in the duration of the P R interval in the two rhythms. Same patients as in Figs. 10 and 11

rhythms are ectopic right atrial rhythms rather than sinus rhythms are based on vectorial analysis of the surface P waves.[1] This analysis shows that the mean P vector which indicates the average orientation of spread of atrial activation points in an inferior leftward and predominantly posterior direction (−60° in the horizontal plane) * Such a direction is compatible with an ectopic focus located somewhere anteriorly and superiorly in the right atrium In sinus rhythm the mean P vector also points inferiorly and to the left but its direction in the horizontal plane is

*The horizontal lead reference frame employed for this computation has been described elsewhere.

much more anterior being more or less perpendicular to the axis of Lead V_1 Accordingly the P waves in sinus rhythm are quite variable in Lead V_1, but are consistently upright in Leads V_3 to V_6. It is important to note that the usual anatomic location of the sinus node at the junction of the superior vena cava with the right atrium,[4,5] with the bulk of the atrial mass in front and to the left of it, precludes this structure as the site of origin of beats whose average direction of propagation is, as in our cases, frankly posterior

Additional evidence which would indicate that the above-described P wave pattern is due to changes in pacemaker site has been found in 9 out of our 19 patients who at other times, had tracings with P wave configuration consistent with sinus origin of impulses (Figs. 9 and 11) In these tracings the P waves were normal both in the extremity leads and in the precordial leads, and their P vector pointed anteriorly inferiorly and to the left—a direction in keeping with the anatomical location of the sinus node.

In addition, in two patients the ectopic right atrial arrhythmias were converted by vagal maneuvers, to normal sinus rhythm and the predicted change in P wave configuration is demonstrated in all 12 leads of the standard ECG (Fig 12)

Discussion

The limitations and advantages of the method employed in the canine experiments have been discussed previously However some aspects of our methodology merit additional comments.

In the isolated cardiac tissue the existence of pacemaking function is based on evidence of spontaneous diastolic phase 4 depolarization In the intact heart, however the demonstration of pacemaker activity is not as well defined Isochronous maps of atrial depolarization during sinus rhythm show the point of earliest activation in the area of the sinus node. Variations from the normal sequence of atrial depolarization may be due either to aberrant conduction or to an ectopic location of the pacemaker With aberrant conduction the point of earliest activation would remain in the area of the sinus node, whereas with ectopic impulse formation it would be found in some other location. The conclusions which we have drawn from our experimental studies are based upon the premise that the recording of initial electrical activity outside the sinus node area suggests ectopic pacemaker activity

It might be argued in this respect that an impulse originating in a structure as large as the sinus node can be delayed in its conduction to an electrode inserted in the region of this node and would therefore appear initially at a more distal recording site. If this were so the consistency of our results would imply that the sinus node electrode was always inserted within a specific region of slow conduction, a rather doubtful possibility Furthermore, previous studies[3] using methods identical to those on which the present investigation is based have demonstrated patterns of atrial activation characterized by initial left atrial activity preceding that recorded by the Bachmann's bundle and by the sinus node electrodes. It seems very unlikely however that sinus impulses could be aberrantly conducted with delay to all recording sites except those in the left atrium. Such a situation would obviously require transmission of the impulse from the sinus node to the left atrium via conduction pathways other than Bachmann's bundle.

Our experimental results provide evidence for the existence of ectopic right atrial rhythm in dogs. The order in which the various atrial recording sites are activated during this rhythm is characteristic and distinctly different from that observed when the sinus node is the site of the pacemaker

Likewise, the sequence of activation during this ectopic rhythm differs from that noted during retrograde conduction when the pacemaker of the heart is located in the ventricles or in the junctional area.[3] During ventriculoatrial conduction initial activity is recorded in the region of the low atrial septum followed next by the regions of the coronary sinus, of Bachmann's bundle and of the sinus node, often with a reversal of the antegrade sequence of the left and right atrial electrograms.

It is of interest to observe that the differ

ences between ectopic right atrial rhythm and sinus rhythm are confined to the early portion of the excitatory process during which right atrial activation occurs. The terminal portion of this process corresponding essentially to left atrial activation is quite similar to that observed during sinus rhythm this probably indicates preservation of the functional role of Bachmann's interatrial band in ectopic right atrial rhythms.[10,11]

In terms of the incidence and of the type of arrhythmias observed the spectrum of right atrial ectopic activity seems to be wide and to resemble that found during our recent study on left atrial automaticity.[2] This observation might be of significance since the experimental conditions during these two studies were identical.

The exact site of impulse formation in ectopic right atrial beats in the dog is uncertain. To obtain more precise information bearing on this question a more detailed mapping of atrial activation would be required. However, the possibility that the pacemaker site is located within or near the right atrial appendage seems reasonable and is supported by the results of RAA pacing which accurately duplicated the sequence of activation observed during ectopic right atrial beats.

Recent microelectrode studies[13,14] support the concept that ectopic rhythms might originate in the right atrium outside the sinus node and the A-V junctional area. Indeed, the presence of latent pacemaker activity in some right atrial fibers was previously noted by Paes de Carvalho and associates[13] and by Hoffman and Cranefield.[13] More recently, Hogan and Davis[14] have found along the caval border of the crista terminalis in the canine right atrium fibers showing diastolic depolarization. The possibility that these fibers may play a role in the genesis of certain types of atrial arrhythmias was considered by these authors. Experiments on isolated right atrial rabbit preparations currently in progress in this laboratory provide the evidence that specialized right atrial fibers can actually become the site of the cardiac pacemaker.[15]

Within this context, our clinical observations acquire particular significance. These observations suggest that ectopic right atrial rhythms represent an electrophysiologic entity and that the impulse forming foci in these rhythms are located somewhere anterosuperiorly in the right atrium.

From a purely electrocardiographic viewpoint the possibility should be considered that the pattern characterized by normal P waves in the extremity leads and inverted P waves in Leads V_1 to V_4 may reflect either changes due to left atrial hypertrophy or a migration of the pacemaker from the upper part of the sinus node to its lower portion rather than an ectopic right atrial rhythm.

The first possibility, although unlikely, should be discussed because left atrial hypertrophy is known to rotate the late P vectors posteriorly in the horizontal plane, a rotation which frequently gives rise to biphasic +−− P waves in Lead V_1[16] and occasionally to a frankly negative deflection in this lead. However, it is difficult to conceive that these abnormal forces could produce a deviation of the mean vector sufficient to invert the P waves beyond Lead V_1 or V_2 and particularly up to V_4. Most of our patients, in addition, did not have any evidence of left atrial hypertrophy. Finally, the disappearance of this pattern under vagal influence (Fig. 12) virtually excludes left atrial hypertrophy as a factor in the genesis of this electrocardiographic syndrome.

Pacemaker migration within the sinus node represents perhaps a more likely possibility. This is so because the sinus node has the considerable length of about 1.5 cm;[6] a displacement of the pacemaker within this structure would necessarily change the orientation of atrial vectors. It has already been pointed out by Levine,[17] however, that such a displacement would deviate the average orientation of atrial activation from a more nearly vertical direction to a more horizontal one, a change which would be reflected by a mean axis change in the frontal plane leads. This was not the situation in our cases in which the average spread of atrial activation had changed from an anterior to a posterior direction, suggesting a shift of the pacemaker along the sagittal rather than the vertical axis. This type of change, moreover, is reflected essentially in the horizontal plane leads.

Thus, this second possibility also appears unlikely.

Recent atrial pacing studies of Harris and associates[18] and of Leon and colleagues[19] support our view that the direction of the mean P vector reflects satisfactorily the site of impulse formation in man. In each instance of their numerous experiments the resultant P wave contour differed from the contour of the normal sinus P wave unless the point of stimulation was adjacent to the sinus node and in every instance the resultant P vector was oriented toward the opposite circumference of the spheroid formed by both atria.

In discussing the degree of correlation between the experimental and clinical data one should recognize, first of all, that the conclusions reached on the basis of our canine experiments are in agreement with those derived from the vectorial analysis of the surface P waves. Both approaches indicated the existence of ectopic right atrial activity and both suggest a similar area as the site from which the impulses originate. Although valid V leads are not obtainable in an open-chest preparation, it is of interest that the characteristics of the ectopic P waves are similar in the human and canine studies: they are consistently upright in Lead II and at the same time distinctly different in shape in this lead from the corresponding upright sinus P waves. These observations suggest that ectopic right atrial rhythms in dogs may represent a counterpart of the human arrhythmia.

Our results are also of interest with regard to the finding of upright P waves in Lead II observed not infrequently in dogs following inactivation of the sinus node.[20] Since under these circumstances the A-V node was generally believed to assume control of the heart,[21] the positivity of the P waves in Lead II (as well as in Leads III and aV) was difficult to understand.[20-22] However, the data reported in this as well as in a previous study demonstrate that elimination of sinus node activity frequently gives rise to atrial rhythms originating outside the A-V junctional area. When these ectopic rhythms originate superiorly in the atria, the P waves are as expected consistently upright in Lead II (Figs. 3 and 4).

This explanation of upright P waves in Lead II by ectopic high atrial activity is also valid in some cases when such P waves follow the QRS complexes induced by ventricular pacing. For example, the first and second paced ventricular beats in Fig. 5 are followed after an identical R-P interval by upright P waves. In the absence of multiple atrial electrograms demonstrating the ectopic right atrial origin of those P waves, one could consider them as reflecting retrograde activation of the atria by a ventricular impulse through the A-V node.

Although our study supports the view that valid inferences regarding the origin of atrial ectopic activity may be drawn from the morphology of the surface P waves, it also shows that the conventional interpretation of tracings which display ectopic right atrial rhythm may result in a mistaken diagnosis of sinus rhythm. These two entities, however, can be readily differentiated if due consideration is given to the characteristics of the P waves in the precordial leads. These leads define approximately the horizontal plane of the body and allow us to infer the direction of atrial activation along the anteroposterior axis. Without this essential information unavailable from extremity leads, the determination of the site of origin of atrial beats and rhythms from surface body leads can be misleading. This point has been emphasized previously[4] and the present report provides additional evidence in its support.

Although typical examples of ectopic right atrial rhythms can be recognized without difficulty, the precise degree of specificity and sensitivity of the electrocardiographic pattern described as suggestive of this arrhythmia remains to be determined. The accuracy of the proposed criteria depends not only upon the site of the pacemaker but also upon several factors not always easily defined. Among these are variability in intra-atrial conduction, the geometry of the atria, their asymmetrical orientation within the chest, inherent limitations of the lead axes systems, errors in electrode placement, and the like. For these reasons we assume that in

some cases of ectopic right atrial rhythm the P wave inversion in the precordial leads may be limited to V_1 through V_3 while in others it may extend beyond V_4 There exists undoubtedly a wide range of modalities by which atrial ectopic activity can express itself in surface body leads and more work is required to bring a clearer understanding into this field

Summary

In 18 out of 25 canine hearts studied with bipolar plunge electrodes ectopic right atrial (RA) beats were observed occurring (1) spontaneously (2) during vagal stimulation (3) after destruction of the sinus node and (4) during ventricular pacing In these beats the RA appendage was activated first followed by Bachmann's bundle sinus node left atrial appendage posterior left atrium and proximal coronary sinus This sequence was consistently reproduced by pacing through the RA appendage recording electrode

In addition 19 electrocardiograms exhibiting normal P waves in the extremity leads and inverted P waves in V_1 to V_4 were subjected to vectorial analysis which indicated the superoanterior RA as the pacemaker site Conversion of these rhythms to sinus rhythm or vice versa was demonstrated It is suggested that this human arrhythmia represents a counterpart of RA ectopic activity observed in the intact canine hearts.

REFERENCES

1 Mirowski, M Antero-superior right atrial rhythms, Israel J Med. Sci. 1:308 1968.
2 Mirowski, M., Lau S H Bobb, G A. Steiner C. and Damato, A. N Studies on left atrial automaticity Circ. Res. 26:317 1970.
3 Damato A N Lau S H. and Bobb G A. Studies on ventriculoatrial conduction and the re-entry phenomenon Circulation 41:423 1970.
4. Scherlag B J Kosowsky B D and Damato A. N A technique for ventricular pacing from the His bundle of the intact heart, J Appl. Physiol. 22:584 1967
5 Mirowski M Left atrial rhythm. Diagnostic criteria and differentiation from nodal arrhythmias, Amer J Cardiol. 17:203 1966.
6. Puech P L'activité électrique auriculaire normale et pathologique, Paris, France, 1956, Masson et Cie.
7 Zimmerman H A Bersano, E., and Dicosky C.: The auricular electrocardiogram, Springfield, Ill 1968 Charles C Thomas, Publisher
8. Barry A. and Bradley P M.: The structure of the adult heart, in Gould, S. E., editor Pathology of the heart, ed 2 Springfield, Ill., 1960 Charles C Thomas, Publisher
9 James, T N Anatomy of the human sinus node, Anat. Rec. 141:109 1961
10. Bachmann, G The interauricular time interval, Amer J Physiol. 41:309 1916.
11 Wagner M L., Lazzara R. Weiss, R. M., and Hoffman, B F: Specialized conducting fibers in the interatrial band Circ. Res. 18:502, 1966.
12 Paes de Carvalho, A. Carlos de Mello, W and Hoffman B F Electrophysiological evidence for specialized fiber types in rabbit atrium, Amer J Physiol. 196:483 1959
13 Hoffman B F and Cranefield P F Electrophysiology of the heart, New York, 1960, McGraw Hill Book Company Inc.
14 Hogan P M and Davis, L. D Evidence for specialized fibers in the canine right atrium, Circ. Res. 23:387 1968.
15. Wit, A. L. Unpublished data.
16. Morris, J J Estes, H Jr Whalen, R. W Thompson, H Jr and McIntosh H. D P wave analysis in valvular heart disease, Circulation 29:242, 1964
17 Levine H D Vagal stimulation in the presence of supraventricular mechanisms, in Dreifus, L. S. and Likoff W editors, Mechanisms and therapy of cardiac arrhythmias, 14th Hahnemann Symposium New York, 1966, Grune & Stratton Inc. p. 167
18 Harris, B C. Shaver J A. Gray S. Kroetz, F W and Leonard, J J Left atrial rhythm Experimental production in man, Circulation 37 1000, 1968
19 Leon, D F Lancaster J F Shaver J A Kroetz F W and Leonard J J Right atrial ectopic rhythms. Experimental production in man, Amer J Cardiol. 25:6, 1970
20. Scherf D and Cohen, J The atrioventricular node and selected cardiac arrhythmias, New York, 1964 Grune & Stratton, Inc.
21 Scherf D Blumenfeld S. and Yildiz, M.: Experimental studies on A V nodal rhythm following suppression of activity of the sinus node, Amer J Cardiol. 10:234 1962.
22 Brumlik, J V The sinoatrial node, the atrioventricular node, and atrial dysrhythmias, in Kossman, C. E. editor Advances in electrocardiography New York, 1958, Grune & Stratton Inc. p. 252.

Role of the nervous system in the arrhythmias produced by coronary occlusion in the cat

Richard A Gillis Ph.D
Washington D C
With the technical assistance of Harold Thibodeaux

A number of reports ha e stressed the importance of the nervous system to changes which occur n cardiac rhythm. First, t has been shown repeatedly that electrical stimulation of brain stem nuclei produces arrhythmias and that these terminate upon cessation of the stimulation Second, electrical stimulation of peripheral nerves to the heart can produce arrhythmias[2,3] Third, drugs which produce arrhythmias, such as digitalis, appear to do so by activation of the nervous system

Evidence for the participation of the nervous system in digitalis induced arrhythmias is particularly well documented For instance it has been shown that cats with sectioned spinal cords are resistant to the arrhythmogenic actions of ouabain and that pharmacologic depression of the sympathetic nervous system e.g by reserpine, confers protection against ouabain cardiotoxicity We recently published proof that ouabain increases both sympathetic and parasympathetic nerve activity in cardiac bound fibers and were able to establish a close correlation between the increased neural activ ty and the occurrence of ventricular arrhythmias.

It has also been suggested that the nervous system contributes to the fatal arrhythmias that follow myocardial infarction, but to date the evidence is largely indirect. For example, several investigators ha e reported that chronic cardiac sympathetic denervation will reduce either occurrence of ventricular arrhythmias or deaths as provoked by coronary occlusion [13,14] and It is well known that atropine sensitive brady-arrhythmias occur commonly in the victims of myocardial infarctions. Direct proof that coronary occlusion excites cardiac bound sympathetic fibers has been sought, but results are contradictory and incomplete. Thus, Costantin [4] found that a decrease in sympathetic nerve activity occurred while Malliani and associates[1] reported an increase in sympathetic nerve activity in both studies, nerve activity was studied only for 1 or 2 min. following temporary occlusion of the coronary artery There is no data to be found regarding the effect of coronary occlusion on efferent parasympathetic nerve firing

The experiments described in this report were done with the objectives of (1) determining the effects of permanent coronary occlusion upon activity in both sympathetic and parasympathetic cardiac bound fibers

From the Department of Pharmacology Georgetown University School of Medicine–School of Dentistry Washington, D. C.

Supported by grants from the United States Public Health Service (HE 0766 FR 5360, and FR 5306) and grant from the Washington Heart Association.

Received for publication Aug 13, 1970.

Reprint requests to: Richard A. Gillis, Ph.D., Department of Pharmacology Georgetown University School of Medicine–School of Dentistry Washington, D. C. 20007

some cases of ectopic right atrial rhythm the P wave inversion in the precordial leads may be limited to V_1 through V_3 while in others it may extend beyond V_4. There exists undoubtedly a wide range of modalities by which atrial ectopic activity can express itself in surface body leads and more work is required to bring a clearer understanding into this field.

Summary

In 18 out of 25 canine hearts studied with bipolar plunge electrodes ectopic right atrial (RA) beats were observed occurring (1) spontaneously (2) during vagal stimulation (3) after destruction of the sinus node and (4) during ventricular pacing. In these beats the RA appendage was activated first followed by Bachmann's bundle sinus node left atrial appendage posterior left atrium and proximal coronary sinus. *This sequence was consistently* reproduced by pacing through the RA appendage recording electrode.

In addition 19 electrocardiograms exhibiting normal P waves in the extremity leads and inverted P waves in V_1 to V_4 were subjected to vectorial analysis which indicated the superoanterior RA as the pacemaker site. Conversion of these rhythms to sinus rhythm or vice versa was demonstrated. It is suggested that this human arrhythmia represents a counterpart of RA ectopic activity observed in the intact canine hearts.

REFERENCES

1. Mirowski, M. Antero-superior right atrial rhythms, Israel J Med Sci. 4:308 1968.
2. Mirowski M *Lau S. H Bobb G. A. Steiner* C. and Damato, A. N Studies on left atrial automaticity Circ. Res. 26:317 1970.
3. Damato A. N Lau, S. H and Bobb G A. Studies on ventriculoatrial conduction and the re-entry phenomenon, Circulation 41:423 1970.
4. Scherlag, B. J Kosowsky B. D and Damato, A. N : A technique for ventricular pacing from the His bundle of the intact heart, J Appl. Physiol. 22:584 1967
5. Mirowski M Left atrial rhythm. Diagnostic criteria *and* differentiation from nodal arrhythmias, Amer J Cardiol. 17:203 1966.
6. Puech P L'activité électrique auriculaire normale et pathologique, Paris, France, 1956, *Masson et Cie.*
7. Zimmerman, H A., Bersano, E., and Dicosky C. The auricular electrocardiogram, Springfield Ill 1968 Charles C Thomas, Publisher
8. Barry A. and Bradley P M The structure of the adult heart, *in* Gould S. E., editor Pathology of the heart, ed. 2 Springfield, Ill., 1960 Charles C Thomas, Publisher
9. James, T N Anatomy of the human sinus node, Anat. Rec. 141:109 1961
10. Bachmann G The interauricular time interval, *Amer J Physiol. 41:309 1916.*
11. Wagner M L., Lazzara, R. Weiss, R. M and Hoffman B F Specialized conducting fibers in the interatrial band Circ. Res. 18:502, 1966.
12. Paes de Carvalho, A. Carlos de Mello, W and Hoffman B. F Electrophysiological evidence for specialized fiber types in rabbit atrium, Amer J Physiol 196:483 1959
13. Hoffman, B F and Cranefield, P F Electrophysiology of the heart New York, 1960, McGraw Hill Book Company Inc.
14. *Hogan, P M and Davis*, L. D Evidence for specialized fibers in the canine right atrium Circ. Res. 23:387 1968.
15. Wit, A. L. Unpublished data.
16. Morris, J J Estes, H., Jr Whalen, R. W Thompson H Jr and McIntosh, H. D P wave analysis in valvular heart disease, Circulation 29:242, 1964
17. Levine H D Vagal stimulation in the presence of supraventricular mechanisms, *in* Dreifus, L. S. and Likoff W editors Mechanisms and therapy of cardiac arrhythmias, 14th Hahnemann Symposium New York, 1966, Grune & Stratton, Inc. p. *167*
18. Harris, B C. Shaver J A. Gray S. Kroetz, F W and Leonard, J J Left atrial rhythm: Experimental production in man, Circulation 37 1000 1968.
19. Leon D F Lancaster J F Shaver J A. Kroetz, F W and Leonard, J J Right atrial ectopic rhythms. Experimental production in man, Amer J Cardiol. 25:6, 1970.
20. Scherf D and Cohen, J The atrioventricular node and selected cardiac arrhythmias, New York 1964 *Grune &* Stratton, Inc.
21. Scherf D Blumenfeld S. and Yildiz, M : Experimental studies on A V nodal rhythm following suppression of activity of the sinus node, Amer J Cardiol. 10:234 1962.
22. Brumlik J V The sinoatrial node, the atrioventricular node, and atrial dysrhythmias, *in* Kossman, C. E. editor Advances in electrocardiography New York, 1958, Grune & Stratton Inc. p. 252.

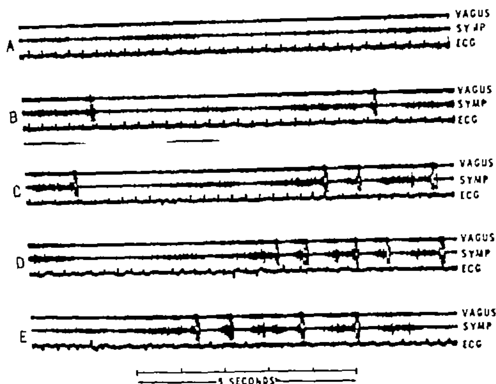


Fig. 1 Effects of coronary occlusion on vagus and sympathetic (*SYMP*) nerve, electrical activity and on the electrocardiogram (*ECG*) of an intact cat. Panel *A* control recordings. Panels *B*, *C*, *D* and *E*, recordings obtained at 1, 2, 3 and 4 min. after the left coronary artery was occluded, respectively

Table I Comparison of data obtained from intact and spinal cats

Parameter	*Neurally intact cats*	*Spinal cats*
Death	81% (17/21)	69% (9/13)
Time of death after coronary occlusion	3.9 ± 0.6 min.	9.1 ± 1.8 min.*
Mode of death		
Ventricular fibrillation	71% (12/17)	20% (2/9)†
Hypotension	29% (5/17)	80% (7/9)
Mean blood pressure		
Control	134 ± 5.9 mm Hg	58 ± 2.5 mm. Hg
Maximal change after occlusion and before arrhythmia	−52 ± 7.9 mm Hg	−33 ± 8.0 mm. Hg
Heart rate		
Control	196 ± 6.0 beats/min	137 ± 4.2 beats/min.
Maximal change after occlusion and before arrhythmia	−33 ± 9.6 beats/min.	+11 ± 11.5 beats/min.

*p 0.02 (Student test).
†p 0.01 (X^2-distribution test).

between coronary occlusion and death was 3.9 min. The changes in blood pressure and heart rate before the arrhythmia appeared also are summarized in Table I. Blood pressure fell in all animals and heart rate usually decreased but in 2 animals did not change. The pattern of these responses is illustrated by the experiment plotted in Fig. 3 wherein simultaneous falls in blood pressure and heart rate occurred within 30 sec. after occlusion and became maximal within 1 min. In this experiment an ar-

and (2) examining whether a relationship exists between nerve activity and cardiac rhythm changes that occur after coronary occlusion

Methods

Experiments were carried out in cats anesthetized with intravenously administered alpha-chloralose 77 mg per kilogram Tracheal cannulation was performed and all animals were ventilated mechanically with room air The chest was opened on both sides by removal of ribs 1 through 6 and preganglionic nerves to the right stellate ganglion were carefully exposed freed and placed on bipolar platinum electrodes. Evidence that these nerves innervated the heart was obtained by electrically stimulating them and demonstrating that tachycardia consistently occurred In each experiment the nerves were sectioned distal to the point where the recording electrodes were placed A thoracic branch of the right vagus nerve also was exposed freed and placed on bipolar platinum electrodes Bradycardia ensued when it was stimulated electrically After testing in this way the branch was sectioned distal to the recording electrodes.

Coronary occlusion was accomplished by dissection of a short length of the main trunk of the left coronary artery and placement of a ligature beneath this vessel This ligature was securely tied at the moment when occlusion was desired

The body temperature of all animals was maintained between 37 0° and 38 5° C with an infrared lamp Femoral blood pressure and Lead I or II of the electrocardiogram (ECG) were recorded continuously In some experiments chloralose-anesthetized cats were subjected to both spinal cord transection at the level of the atlanto-occipital interspace (C 1) and bilateral cervical vagotomy

Results

The effects of coronary occlusion were studied in 21 animals with intact nervous systems. Neural activity was monitored from the sympathetic preganglionic fibers in 16 of them and was found to increase above control level immediately after occlu[illegible] 13 A representative experiment showing this increase appears in Fig 1 During the control period neural activity appeared in a regularly occurring bursting pattern with a constant amplitude. Within 1 min after occlusion the activity increased in amplitude and within 2 min it became more frequent and irregular These changes were exaggerated with time Associated with them were changes in the ECG. Within 2 min after occlusion the regular ECG pattern was disrupted and arrhythmias appeared These terminated in ventricular fibrillation about 5 min after occlusion In 3 of the 16 experiments, there was no increase in sympathetic nerve activity That is, no change occurred until the heart began to fibrillate At the time of fibrillation nerve activity became greatly augmented

Similar changes occurred in 12 of the 14 animals in which parasympathetic nerve activity was monitored As illustrated in Fig 1 during the control period the activity in the parasympathetic nerve occurred in a regular bursting pattern which was less frequent but similar in duration to the sympathetic Within 1 min after occlusion of the coronary artery parasympathetic activity increased in amplitude and within 2 min became more frequent and irregular the frequency of the bursts matched that in the sympathetic nerve recordings and firing in both autonomic nerves was synchronous. Arrhythmias began within 2 min after occlusion Two animals showed no change in parasympathetic activity until ventricular fibrillation at which time the activity increased In most animals in which activity increased after occlusion the increase persisted until death but in 3 the activity decreased below base level when the arrhythmias began and did not again increase until ventricular fibrillation

ECG changes associated with the increased autonomic activity included bradycardia ventricular premature contractions, and ventricular tachycardia In 3 experiments pretreatment with 1 0 mg per kilogram of atropine completely prevented the slowing in heart rate associated with coronary occlusion

As shown in Table I 81 per cent of the animals with intact nervous systems died 12 because of ventricular fibrillation and 5 because of hypotension T[illegible] average time

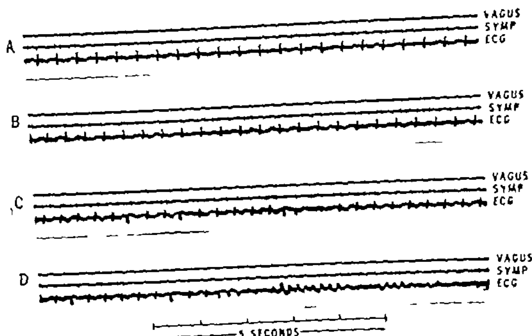


Fig. 4 Effects of coronary occlusion on vagus and sympathetic nerv electrical activity and on the ECG of a spinal cat. Panel *A* control recordings Panels *B* *C* and *D* recordings obtained at 1, 2, and 3 min. after the left coronary artery was occluded, respectively

monitored before during and after tying off the tissue The procedure had no significant effect on any of these parameters.

The effects of coronary occlusion also were studied in 13 animals with sectioned spinal cords and vagus nerves. Neural activity was monitored from the sympathetic preganglionic fibers only in 10 animals and from both sympathetic and parasympathetic fibers in 3 animals. During the control period the sympathetic neurogram usually registered random low level activity or no activity and the parasympathetic neurogram registered no activity (Fig 4) After coronary occlusion, parasympathetic nerve activity remained absent, and sympathetic activity was essentially unchanged. ECG changes, consisting of ventricular extrasystoles, occurred later in time than in the intact animals.

As shown in Table I 69 per cent of these spinal animals died The 4 survivors developed ventricular extrasystoles which disappeared within 1 hr after occlusion. In comparison to the intact nervous system group, fewer animals of the neurally deprived series died from ventricular fibrillation (71 per cent versus 20 per cent) Moreover the average time to death after occlusion was 9 1 min. in the neurally deprived cats and 3 9 min for the neurally intact animals. These differences are significant ($p < 0.01$ and $p < 0.02$ respectively)

The changes in blood pressure and heart rate induced by coronary occlusion in these cats with sectioned spinal cords and vagus nerves are summarized in Table I The initial pressures and heart rates were significantly lower ($p < 0.01$) than in the controls and an additional fall in blood pressure after coronary occlusion occurred in 9 of the 13 animals. A biphasic change (an initial increase followed by a decrease) was observed in the other 4 A small increase in heart rate occurred in most animals after occlusion. The pattern of these responses is illustrated in the experiment plotted as part of Fig 3 As can be seen, the blood pressure showed a slight increase in the first 30 sec. after occlusion but then declined, reaching a nadir within 2 min. Heart rate remained unchanged until 3 min. after occlusion when a distinct increase occurred. This increase was maintained until the arrhythmia developed.

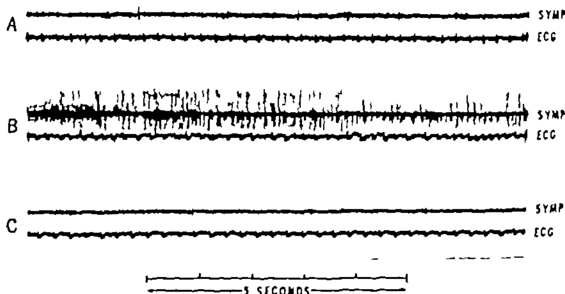


Fig. Effects of coronary occlusion on sympathetic nerve electrical activity and on the ECG of an intact cat. Panel A control recordings. Panels B and C recordings obtained at 12 and 33 min. after the left coronary artery was occluded respectively.

rhythmia appeared within 3 min and ventricular fibrillation and death within 4.5 min. As illustrated, the onset of the arrhythmia coincided with a further drop in blood pressure.

The 4 survivors (19 per cent) showed S-T–T wave changes consisting of depression in 3 instances and elevation in the other instance. Ventricular extrasystoles occurred in all 4 animals. In 3 of the 4 ventricular extrasystoles disappeared within 1 hr but the S-T–T wave changes persisted. In the fourth animal the ventricular extrasystoles induced by coronary occlusion persisted for the duration of the experiment. Fig. 2 shows an experiment representative of the 3 in which sinus rhythm returned spontaneously. Very little sympathetic neural activity occurred during the control period. However, coronary occlusion resulted in sympathetic activation which reached its peak 12 min after occlusion and was associated with runs of ventricular tachycardia. Eventually both the sympathetic neural activity and the rhythm simultaneously returned to normal; only a depression of the S-T wave remained.

Two experiments were performed in which a ligature was passed around tissue close to the left coronary artery but not around the artery itself. Sympathetic nerve activity, ECG, and blood pressure were

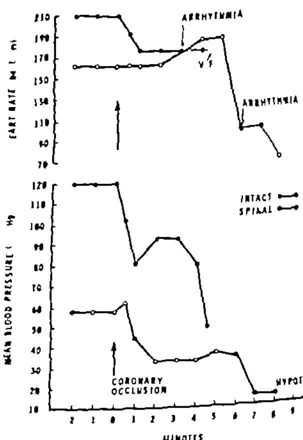


Fig. 3. Effects of coronary occlusion on the heart rate and blood pressure readings of (1) an animal with its nervous system intact and (2) an animal with its spinal cord and cardiac vagus nerves sectioned. VF and HYPOT refer to ventricular fibrillation and hypotension, respectively, and was the mode of death in the designated animal.

cardioregulatory areas. Evidence for a sympathetic-enhancing reflex in coronary occlusion has been presented by Brown[26] and Malliani and co-workers,[27] and for a vagal reflex of cardiac origin by Ascanio and associates,[27] and Kolatat and co-workers.[28] A seemingly related example for an autonomic reflex initiated by activation of afferent sensory fibers occurs after the administration of digitalis. We have shown that in addition to its better known effects on the heart, digitalis acts to increase activity in the autonomic nervous system. At least part of this activity arises from activation of sensory fibers in the heart[29] and in the nodose ganglia.[30] As in the case of the increased autonomic nerve activity caused by coronary occlusion, the increase produced by digitalis is related to the onset of ventricular arrhythmias.

These results suggest that the overriding consideration for antiarrhythmic drug therapy in patients may be to quiet the nervous system so as to prevent the excitation of the autonomic nervous system. This could be done with centrally acting neural depressants, as has been suggested from time to time[31-34] or by suppressing the effects of the autonomic overactivity. As noted above, atropine has been reported to be highly effective in dealing with the arrhythmogenic activity of the parasympathetic system but as pointed out by Adgey and co-workers,[35] the importance of atropine in the management of acute infarction is largely unrecognized. However the use of atropine can be a disadvantage in situations where generation of impulses from the S-A node occurs, but A-V nodal disease exists.[36] Under these conditions the atrial rate may greatly increase but so may the degree of A-V block, and a consequent decrease in ventricular rate may be the outcome (see Fig. 6A of Danzig and associates[5])

A variety of agents are available to block the effects of the adrenergic nervous system but none of these are as selective as atropine and therefore are not as safe to use. Further more, there is controversy over their mechanism of action some investigators believe that their effects on the nervous system are more important than their effects on beta adrenergic receptors.[36] New agents are being developed e.g. the recently introduced "cardioselective agent," practolol[37] and it is possible that one of these in conjunction with atropine may prove to be the most efficacious way of dealing with the arrhythmias that follow a myocardial infarction.

Summary

The importance of the nervous system in the arrhythmias generated by occlusion of the left coronary artery of the cat was investigated. This was carried out by (1) monitoring the spontaneous electrical activity in sympathetic and parasympathetic cardiac nerves and (2) determining the influence of ablation of the nervous system on time taken for death to occur and on incidence of ventricular fibrillation. It was found that coronary occlusion increased the spontaneous firing in cardiac-bound autonomic fibers and that the enhanced neural activity was correlated in time with electrocardiographic changes consisting of ventricular arrhythmias. Removal of the central nervous system and both vagi conferred protection against arrhythmogenesis. Animals with no neural input to the heart (as indicated by the nerve recordings) survived more than twice as long after coronary occlusion and showed a significant reduction in the incidence of ventricular fibrillation. These results suggest that the nervous system plays an important role in the generation of arrhythmias produced by coronary occlusion in the cat.

The author wishes to express his appreciation to Professor Frank G. Standaert for his help in the preparation of this manuscript.

REFERENCES

1. Manck, H. P., and Hockman, C. J.: Central nervous system mechanisms mediating cardiac rate and rhythm, Amer. Heart J. 74:96, 1967.
2. Manning, J. W., and Cotten, M. deV.: Mechanisms of cardiac arrhythmias induced by diencephalic stimulation, Amer. J. Physiol. 203:1120, 1962.
3. Raper, C., and Wale, J.: Cardiac arrhythmias produced by interaction of ouabain and beta-receptor stimulation, European J. Pharmacol. 6:223, 1969.
4. Levitt, B., Raines, A., Sohn, Y. J., Standaert, F. G., and Hirshfeld, J. W.: The nervous system as a site of action for digitalis and antiarrhythmic drugs, J. Mount Sinai Hosp., N. Y. 37:227, 1970.

Discussion

These results provide direct evidence that coronary occlusion excites cardiac bound autonomic nerve fibers and that the increased neural activity is closely associated with the development of arrhythmias. In the animals which survived coronary occlusion restoration of sinus rhythm was correlated with resumption of normal patterns of nerve activity

Other investigators have made direct measurements of the effects of coronary occlusion on efferent sympathetic nerve firing in cats. Malliani and co-workers[17] found that during the first 2 min after occlusion only an increase or no change in spontaneous activity occurred in 8 sympathetic nerve preparations. Occlusion was maintained for a maximum of 2 min after the release of the occluding ligature the nerve activity returned to normal Costantin[18] found the opposite in his experiments with temporary (no longer than 2 min) coronary occlusion that is, sympathetic efferent activity to the heart was decreased The reason for the inconsistency in their results is not clear The present results are similar to those of Malliani and associates[17] in that sympathetic nerve firing was either enhanced (81 per cent) or unchanged (19 per cent) In addition they provide evidence that the parasympathetic system is activated simultaneously with the sympathetic and that the increased autonomic activity is correlated with alterations in rhythm

Evidence that autonomic nerve function is exaggerated after myocardial infarction and that the increased neural activity is related to arrhythmogenesis can also be found in studies on human beings. For example several reports indicate that increased levels of plasma and urinary norepinephrine levels are present in many patients with myocardial infarction[18] and that there is a close relationship between high levels of catecholamines and high incidence of arrhythmias.[19,20] Exaggerated parasympathetic neural activity following myocardial infarction has also been reported to occur in man For instance in a study of 400 patients, Adgey and co-workers[21] found that 61 per cent developed bradyarrhythmias. These investigators also found atropine to be effective in the management of these arrhythmias an indication that they were caused by excessive vagal discharge

Evidence that the relationship between the onset of arrhythmias and the activation of the nervous system is more than coincidental derives from several sources. Ebert and associates[14] and Schaal and co-workers[15] reported that extrinsic cardiac denervation by the mediastinal neural ablation technique of Cooper and associates[22] protects against arrhythmias produced by coronary occlusion Others have shown that the infarcted heart is more sensitive to the arrhythmogenic effects of catecholamines[23] and of vagal overactivity.[24] The observation (Fig 1) that simultaneous activation of both sympathetic and parasympathetic fibers occurs after coronary occlusion is of particular interest because it has been shown that simultaneous activation of both branches of the autonomic nervous system provides a more potent arrhythmogenic stimulus than activation of either branch alone.[2] Finally there is the observation that removal of the central nervous system and both vagi conferred protection against arrhythmogenesis (Table I) Animals with no neural input to the heart survived more than twice as long after infarction and showed a significant reduction in the incidence of ventricular fibrillation An alternative possibility that the protective effect is an indirect one caused by the reduction in blood pressure that accompanies these procedures, is unlikely since it has been shown that hypotension of this magnitude tends to increase ventricular ectopic frequency.[25]

The mechanism whereby coronary occlusion activates efferent sympathetic nerves was not sought in our experiments, but two possibilities exist One is that activation may occur because of the associated hypotension and the resultant baroreceptor response to the pressure change This might explain the increased sympathetic activity but is not likely to be the cause of the increased vagal activity because hypotension should reduce parasympathetic tone. The alternative is that coronary occlusion may excite afferent sensory fibers and cause reflexly enhanced activity in the central

cardioregulatory areas. Evidence for a sympathetic-enhancing reflex in coronary occlusion has been presented by Brown[16] and Malliani and co-workers,[1] and for a vagal reflex of cardiac origin by Ascanio and associates,[17] and Kolatat and co-workers.[18] A seemingly related example for an autonomic reflex initiated by activation of afferent sensory fibers occurs after the administration of digitalis. We have shown that in addition to its better known effects on the heart, digitalis acts to increase activity in the autonomic nervous system.[4] At least part of this activity arises from activation of sensory fibers in the heart[19] and in the nodose ganglia.[20] As in the case of the increased autonomic nerve activity caused by coronary occlusion the increase produced by digitalis is related to the onset of ventricular arrhythmias.

These results suggest that the overriding consideration for antiarrhythmic drug therapy in patients may be to quiet the nervous system so as to prevent the excitation of the autonomic nervous system. This could be done with centrally acting neural depressants, as has been suggested from time to time[21-24] or by suppressing the effects of the autonomic overactivity. As noted above, atropine has been reported to be highly effective in dealing with the arrhythmogenic activity of the parasympathetic system but as pointed out by Adgey and co-workers,[11] the importance of atropine in the management of acute infarction is largely unrecognized. However the use of atropine can be a disadvantage in situations where generation of impulses from the S-A node occurs, but A-V nodal disease exists.[25] Under these conditions the atrial rate may greatly increase but so may the degree of A V block, and a consequent decrease in ventricular rate may be the outcome (see Fig 6A of Danzig and associates[25])

A variety of agents are available to block the effects of the adrenergic nervous system but none of these are as selective as atropine and therefore are not as safe to use. Further more, there is controversy over their mechanism of action some investigators believe that their effects on the nervous system are more important than their effects on beta-adrenergic receptors.[26] New agents are being developed e.g., the recently introduced "cardioselective agent," practolol,[27] and it is possible that one of these in conjunction with atropine may prove to be the most efficacious way of dealing with the arrhythmias that follow a myocardial infarction.

Summary

The importance of the nervous system in the arrhythmias generated by occlusion of the left coronary artery of the cat was investigated. This was carried out by (1) monitoring the spontaneous electrical activity in sympathetic and parasympathetic cardiac nerves and (2) determining the influence of ablation of the nervous system on time taken for death to occur and on incidence of ventricular fibrillation. It was found that coronary occlusion increased the spontaneous firing in cardiac-bound autonomic fibers and that the enhanced neural activity was correlated in time with electrocardiographic changes consisting of ventricular arrhythmias. Removal of the central nervous system and both vagi conferred protection against arrhythmogenesis. Animals with no neural input to the heart (as indicated by the nerve recordings) survived more than twice as long after coronary occlusion and showed a significant reduction in the incidence of ventricular fibrillation. These results suggest that the nervous system plays an important role in the generation of arrhythmias produced by coronary occlusion in the cat.

The author wishes to express his appreciation to Professor Frank G. Standaert for his help in the preparation of this manuscript.

REFERENCES

1. Mauck, H. P and Hockman, C. J Central nervous system mechanisms mediating cardiac rate and rhythm, Amer. Heart J 74:96, 1967
2. Manning, J W and Cotten, M. deV Mechanism of cardiac arrhythmias induced by diencephalic stimulation, Amer J Physiol. 203:1120, 1962.
3. Raper C., and Wale, J Cardiac arrhythmias produced by interaction of ouabain and beta-receptor stimulation, European J Pharmacol. 6:223, 1969
4. Levitt, B., Raines, A., Sohn, Y J Standaert, F G., and Hirshfeld, J W The nervous system as site of action for digitalis and antiarrhythmic drugs, J Mount Sinai Hosp N Y 37:227 1970.

5. Boyajy L. D and Nash C. B Alteration of ouabain toxicity by cardiac denervation Toxic. Appl Pharmacol. 9:199 1966.
6. Raines, A. Levitt, B and Standaert, F G The effect of spinal section on ventricular rhythm disorders induced by ouabain, Arch. Int. Pharmacodyn. 1 0:485 1967
7. Gillis, R. A. Levitt B Raines, A. Sohn, Y J and Standaert, F G. Effect of ouabain on sympathetic, vagus, and phrenic nerve activity Pharmacologist 11:244 1969
8. Roberts, J Pharmacologically induced depression of adrenergic nervous activity in the heart *in* Tanz, R. D., Kavaler F and Roberts, J., editors. *Factors influencing myocardial contractility* New York, 1967 Academic Press, Inc. p. 489
9. Gillis, R. A. Cardiac sympathetic nerve activity—changes induced by ouabain and propranolol, Science 166:508 1969
10. Harris, A. S. Factors which determine prognosis in experimental coronary occlusion *in* Surowicz, B and Pellegrino, E. D., editors Sudden cardiac death New York, 1964 Grune & Stratton, Inc p. 110.
11. Harris, A. S Genesis of ventricular tachycardia and fibrillation following coronary occlusion, *in* Dreifus, L. S., and Likoff W editors Mechanisms and therapy of cardiac arrhythmias, New York, 1966 Grune & Stratton Inc., p. 293.
12. Cox W V and Robertson, H F The effect of stellate ganglionectomy on the cardiac function of intact dogs, Amer. Heart J 12:285 1936.
13. Harris, A. S., Estrandia, A., and Tillotson R. F Ventricular fibrillation following cardiac sympathectomy and coronary occlusion, Amer J Physiol. 165:505 1951
14. Ebert, P A. Allgood R. J and Sabiston D C. Jr: The antiarrhythmic effects of cardiac denervation, Ann. Surg 168 728, 1968
15. Schaal S. F., Wallace A. G and Sealy W C Protective influence of cardiac denervation against arrhythmias of myocardial infarction Cardiovasc. Res. 3:241 1969
16. Costantin, L. Extracardiac factors contributing to hypotension during coronary occlusion, Amer J Cardiol. 11:205 1963
17. Malliani, A., Schwartz, P J and Zanchetti A. A sympathetic reflex elicited by experimental coronary occlusion Amer J Physiol. 217:703 1969
18. Gazes, P C., Richardson, J A. and Woods, E. F Plasma catecholamine concentrations in myocardial infarction and angina pectoris, Circulation 19:657 1959
19. Klein R. F Troyer W G Thompson, H K. Bogdonoff M. D., and Wallace, A. G Catecholamine excretion in myocardial infarction, Arch. Intern. Med. 122:476, 1968.
20. McDonald, L., Baker C. Bray C. McDonald A., and Restieaux, N: Plasma catecholamines after cardiac infarction, Lancet 2:1021 1969
21. Adgey A. A. J Geddes, J S., Mulholland H. C. and Keegan, D A. J: Incidence, significance, and management of early bradyarrhythmia complicating acute myocardial infarction, Lancet 2:1097 1968
22. Cooper T., Gilbert, J W., Jr., Bloodwell, R. D., and Crout, R. J Chronic extrinsic cardiac denervation by regional neural ablation. Description of the operation, verification of the denervation and its effects on myocardial catecholamines, Circ. Res. 9:275 1961
23. Maling H. M and Moran, N C. Ventricular arrhythmias induced by sympathomimetic amines in unanesthetized dogs following coronary artery occlusion, Circ. Res. 5:409 1957
24. Braun, L., and Samet, B. "Vagusdruck und Koronargefass. (Ein klinischer und experimenteller Beitrag zur Diagnose und Prognose der Herzkrankheiten) Arch. Klin. Med. 161:257 1928.
25. Harris, A. S. Otsuka, H and Boggs, P B. Changes in infarction arrhythmias resulting from changes in arterial pressure, Amer J Physiol. 210:526, 1966.
26. Brown, A. M Excitation of afferent cardiac sympathetic nerve fibers during myocardial ischaemia, J Physiol. 190:35 1967
27. Ascanio, G. Barrera, F Lautsch, E. V and Oppenheimer M J Role of reflexes following myocardial necrobiosis, Amer J Physiol. 209 1081 1965
28. Kolatat, T Ascanio, G Tallarida, R. J and Oppenheimer M J Action potentials in the sensory vagus at the time of coronary infarction, Amer J Physiol. 213 71 1967
29. Sleight P Lall A. and Muers, M Reflex cardiovascular effects of epicardial stimulation by acetylstrophanthidin in dogs, Circ. Res. 25 705 1969
30. Chai C. Y., Wang, H. H Hoffman, B. F and Wang S. C. Mechanisms of bradycardia induced by digitalis substances, Amer J Physiol. 212:26, 1967
31. Gold H. Treatment of cardiac arrhythmias, Med Clin. N Amer 24:577 1940.
32. Sabathie, L. G. On the intravenous use of morphine in the treatment of paroxysmal ventricular tachycardia Amer. Heart J 33 719 1947
33. Mosey L. and Stutzman, J W The effect of cyclopropane, ether and thiopental sodium upon the over-digitalized heart Proc. Soc. Exp. Biol. Med. 73:34 1950.
34. Nixon, P G. F., Taylor D J E. Morton, S. D and Bromfield M A sleep regimen for acute myocardial infarction, Lancet 1 726, 1968
35. Danzig R. Alpern, H., and Swan, H. J C. The significance of atrial rate in patients with atrioventricular conduction abnormalities complicating acute myocardial infarction, Amer J Cardiol. 24:707 1969.
36. Standaert F G. Levitt, B. Roberts, J and Raines, A.: Antagonism of ventricular arrhythmias induced by digitalis—A neural phenomenon, Europ. J Pharmacol. 6:209 1969.
37. Jewitt D E., Mercer C. J and Shillingford, J P Practolol in the treatment of cardiac dysrhythmias due to acute myocardial infarction, Lancet 2:227 1969

Case reports

Untreated (combined) intracardiac and valvular trauma with long asymptomatic survival

F. L. Ehrenstein, M.D.
R. C. Bahler, M.D.
J. Ankeny, M.D.
H. Schwartz, M.D.
Cleveland, Ohio

Since Rehn's[1] original communication (1897) numerous heroic and successful repairs of cardiac and great vessel injuries have been performed. Patients with cardiac trauma who survive the immediate posttraumatic period usually have sustained only a myocardial laceration or contusion-lesions which can be easily managed, complete recovery being the rule. Rare are those, however, who survive intracardiac, valvular, or combined lesions long enough to undergo corrective surgery. The following case report illustrates the unusual combination of an intracardiac shunt and a valvular laceration associated with a surprisingly benign 17 year course.

Case report

A 47 year-old Negro man was first admitted to the Cleveland Veterans Administration Hospital on April 10, 1968, because of breathlessness, nocturnal dyspnea, and massive leg edema. He was asymptomatic, working daily as a construction laborer until two months before admission. He enjoyed good health all his life except for a chest and an abdominal stab wound in October 1952, the latter necessitating emergency abdominal exploration with repair of liver and gastric lacerations. The laceration in the chest was midsternal at the level of the fourth costochondral junction, and did not require suturing. Several days after the incident a machinery murmur best heard at the left cardiac base, was described by one examiner. Chest x-ray film was normal and the cardiothoracic ratio was 13/33 cm. Cardiac catheterization was unsuccessful. Being asymptomatic, he was discharged without specific recommendations.

On the present admission, 17 years later, mild respiratory distress was evident. The blood pressure was 150/50 and the pulse 90, regular and bounding. The jugular veins filled to the mandibular angle at 45 degrees. A faint 1 cm. scar was present over the midsternum at the fourth intercostal space. Auscultation revealed a normal S_1 and single S_2, a Grade 4/6 continuous murmur loudest in the third left intercostal space, a Grade 3/6 decrescendo diastolic murmur at both lower sternal borders, and a Grade 3/6 basilar systolic ejection murmur radiating to the neck. Crepitant râles were present at both lung bases, the liver extended 12 cm. below the right costal margin, and he had severe leg edema.

Chest x-ray film showed massive cardiomegaly and pulmonary congestion (Fig. 1, *A*). Electrocardiogram revealed sinus rhythm, first degree A-V block, and left ventricular hypertrophy.

Bed rest, salt restriction, digitalis, and hydrochlorothiazide led to a 60 pound weight loss and complete disappearance of symptoms. Cardiac

From the Departments of Medicine and Thoracic Surgery of Case Western Reserve University School of Medicine at the Veterans Administration Hospital, 10701 East Blvd., Cleveland, Ohio.

Received for publication March 16, 1970.

Reprint requests to: R. C. Bahler, M.D., Cardiology Section, Veterans Administration Hospital, 10701 East Blvd., Cleveland, Ohio 44106.

*Current address: Fred L. Ehrenstein, M.D., Lieutenant Commander (MC)USNR, Department of Surgery, Naval Hospital Memphis, Millington, Tenn. 38054.



Fig 1 *A* Generalized cardiomegaly and prominent pulmonary vasculature are present. The cardiothoracic ratio is 21/33 cm. *B* The cardiothoracic ratio is now 17/33 cm the aorta remains dilated and the vasculature is normal

catheterization demonstrated a left to-right shunt at the ventricular level The pulmonary artery pressure was 38/14 mm Hg and the pulmonary to systemic flow ratio was 2 5 1 The shunt site was verified when the aortic catheter entered the right ventricle A root angiogram outlined the aortic-right ventricular fistula and demonstrated severe valvular aortic regurgitation. On May 2 1969 the heart was exposed through a midline sternotomy No pericardial adhesions were present A thinned 2 cm. portion of the right ventricular outflow tract was the site of paradoxical pulsations and a continuous thrill A diastolic thrill was felt over the dilated aortic root All cardiac chambers were massively enlarged Following institution of cardiopulmonary bypass the aneurysmal portion of the right ventricular outflow tract was widely opened. A 15 mm. fibrous defect located high in the interventricular septum and communicating with the right sinus of Valsalva, was easily repaired. Exposure of the aortic valve revealed a laceration of the right cusp, its free margin dangling unsupported (Fig 2) A competent bicuspid valve was fashioned by suturing the right and left cusps together The postoperative course was uneventful. He returned to work as a laborer and has been asymptomatic. Eight months after surgery his blood pressure was 140/75 mm. Hg and a Grade 2/4 early diastolic murmur remained The cardiac size was decreased (Fig 1 *B*)

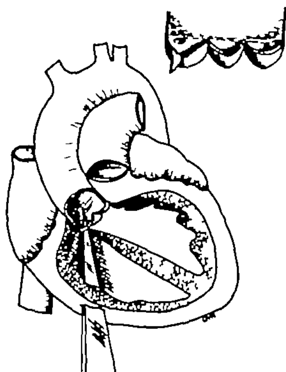


Fig 2 The course of the stab wound and resulting right coronary cusp laceration are illustrated

Discussion

Aortic insufficiency as well as intracardiac communications occur as a result of blunt[3-7] and penetrating[8-12] injuries and each can be successfully managed The combination of valvular damage plus a traumatic intracardiac shunt[13,14] is rarely amenable to repair since few of the victims survive long enough to seek treatment. This is illustrated by the report of Beall and co-workers[17] who had no patients with combined valvular and intracardiac

trauma among 177 patients seeking treatment for cardiac injuries, and only 5 patients with *shunts and one* with aortic regurgitation. In a follow-up of 40 World War II veterans who survived cardiac *missile wounds, there* were no intracardiac communications and only one case of valvular trauma again stressing the rarity of survival with intracardiac and valvular lesions.[18] Individuals sustaining such injuries and surviving the immediate post traumatic period rapidly develop relentless cardiac decompensation requiring *early definitive treatment,*[16,1] or dying from congestive failure within a short period of time. It is the 17 year asymptomatic interval following a generally fatal injury that makes our case unique. Mulder[13] described a similar patient whose lesion was corrected 10 years after he had been stabbed. Bacterial endocarditis at *the fistula site necessitated the repair* To the best of our knowledge these are the only two published cases of prolonged survival following such complex cardiac injuries.

Summary

A 47 year-old man experienced an exceptional 17 year *asymptomatic interval* following a cardiac stab wound which created an aortic-right ventricular fistula and a lacerated incompetent aortic valve, a combination of lesions which is generally fatal.

REFERENCES

1. Rehn, L. Uber Penetrirende Herzwunden und *Herznaht*, Arch Klin. Chir 55:315 1897
2. Beall, A. C J and Shirley A L. Successful surgical correction of traumatic aortic valve regurgitation, J.A.M.A. 187:507 1964.
3. Levine, R J Roberts, W C., and Morrow A. G. Traumatic aortic regurgitation, Amer J Cardiol. 10 752, 1962.
4. Bean, W B., and Mohaupt, F X. Rupture of the aortic valve, J.A.M A. 150:92, 1952.
5. Leonard J J Harvey W P and Hufnagel, C. A.: *Rupture* of the aortic valve. A therapeutic approach, New Eng. J Med. 252:208, 1955.
6. Gregersen H., and Nielsen, K. Traumatic rupture of *the aortic* valve, *Acta* Chir Scand. 129:669 1965
7. Miller *D R., Crockett, J E. and Potter C.* A.: Traumatic interventricular septal defect, A review and report of t o cases, Ann. Surg. 155 72, 1962.
8. Cleveland, R. J Kemp, V E., and Lowe, R. R. Acute aortic insufficiency as result of a bullet wound. Report of a case of successful treatment, J Thorac. Cardiovasc. Surg. 53 123 1968.
9. Norman, J C., Weber W J Wilson, W S., and Sloan, H. Post traumatic fistula of the aorta, pulmonary artery and right ventricle, Ann. Surg. 161:357 1965.
10. King, H., and Schumacher H. B. Surgical repair of traumatic aortic-right ventricular fistula, J Thorac. Surg. 35:734, 1958.
11. Hardy J D and Timmis, H. H.: Repair of *intracardiac gunshot injuries. Report of three* cases, Ann. Surg. 169:906, 1969
12. *Summerall, C. P Lee, W H., and Boone, J A..* I tracardiac shunts after penetrating wounds of *the* heart, New Eng J Med. 272:240, 1965.
13. Mulder D G. Stab wound of the heart, Ann. Surg. *160:287* 1964.
14. Berger R. L., Gibson, H., Riemer R. W and *Ramaswamy* K.: Traumatic aortic regurgitation, ventricular septal defect, and fistula of the sinus of Valsalva, New Eng. J Med. 281 887 1969
15. Parmley L. F Mattingly T W and Manion, W C. Penetrating wounds of the heart and aorta, Circulation 17:953, 1958.
16. Kanber G. J Fort, M. L., Treger A., Meadows, W R., and Sharp, J T Left ventricular right trial canal with aortic Incompetence of probable traumatic origin, Amer J Cardiol. 20:879 1967
17. Beall, A. C., J Hanlt, H. F Cooley D A and DeBakey M. E. Surgical management of traumatic intracardiac lesions, J Trauma 5:133 1965.
18. Bland, E. F and Beebe, G. W Missiles in the heart. A twenty year *follow-up* report of World War II cases, New Eng. J Med. 274 1039 1966.
19. Gerbode, F Treatment of emergencies of the heart and great vessels, J.A.M.A. 156:898, 1954.

Double-outlet left ventricle with ventricular septal defect and pulmonary stenosis Report of surgical repair

Alan R. Kerr, M.B., Ch.B.
Alberto Barcia, M.D.
L. M. Bargeron, Jr., M.D.
John W. Kirklin, M.D.
Birmingham, Ala.

Origin of the aorta and pulmonary artery from the right ventricle (double outlet right ventricle) is a recognized congenital cardiac malformation. In one variant of this the ventricles are inverted and the morphologic right ventricle is functionally the left ventricle.[1-3] The analogous condition involving the morphologic left ventricle is extremely uncommon. Sakakibara and associates[4] reported on the surgical correction of a patient with high large subpulmonary ventricular septal defect without pulmonary stenosis and both great arteries originating from the morphologic left ventricle. Recently Van Praagh and associates[5] described the anatomical characteristics of true double outlet left ventricle with intact ventricular septum and hypoplastic right ventricle. They also discussed the developmental implications that determine the malformation.

Our report concerns the successful surgical treatment of one patient with double outlet left ventricle with extreme underdevelopment of the infundibulum (conus) of the right ventricle, large subaortic ventricular septal defect, and severe pulmonary valvular stenosis. The details of the malformation are quite different from those in the case reported by Sakakibara and colleagues. The preoperative diagnosis of this condition and differentiation from tetralogy of Fallot depend on high quality large film selective biplane angiocardiography with injections into both right and left ventricle.

Case report

A 3½-year-old boy was first seen at the University of Alabama Medical Center in 1968 because of cyanotic congenital heart disease. He was the product of a normal pregnancy and delivery and cyanosis was noted following birth. Three older siblings were normal. A right Blalock-Taussig anastomosis was performed elsewhere when he was 10 months of age. This failed to function, and when the patient was 11 months old, a similar procedure was performed on the left. The child subsequently was

From the Departments of Surgery, Radiology and Pediatrics, The School of Medicine and the Medical Center, University of Alabama in Birmingham, Birmingham, Ala.
Received for publication March 16, 1970.
Reprint requests to: John W. Kirklin, M.D., Department of Surgery, University of Alabama in Birmingham, Medical Center, 1919 Seventh Ave., Birmingham, Ala. 35233.

 May 1971 Vol. 81 No. 5 pp. 688-693

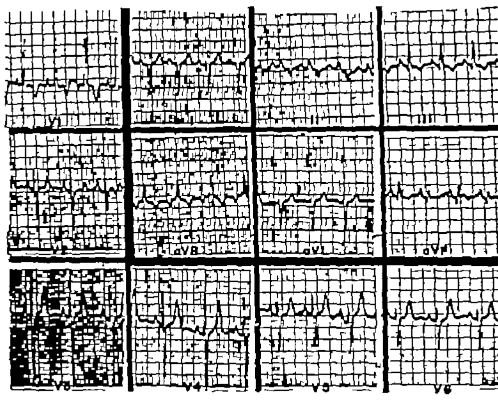


Fig. 1A. Electrocardiogram showing severe right ventricular hypertrophy as manifested in V by a tall R wave and negative T wave. The initial forces in this and in the vectorcardiogram in Fig. 1 *B-D* suggest normally oriented septal depolarization. (1 mv = 2 cm.)

less cyanotic and more active although no definite continuous murmur was heard. *Progress was satisfactory* until one year before admission when effort intolerance and cyanosis increased. He did not squat, but had suffered *three* hypoxic spells.

Examination showed a rather obese, intensely cyanotic boy with marked clubbing. Carotid pulsations were normal, and blood pressure in the arms unobtainable. There was a Grade 1 left parasternal heave, a systolic thrill, and a Grade 4 harsh systolic ejection murmur maximal in the third left intercostal space (all grading is on the basis of 1 to 6). His hematocrit was 73 per cent. The electrocardiogram and vectorcardiogram are shown in Fig. 1. The conventional chest roentgenogram (Fig. 2) showed situs solitus of the viscera and atria. The heart volume in relation to body surface area was mildly increased. The configuration of the heart with an upturned apex and straight *left* border was like that usually seen in tetralogy of Fallot. The right atrium was dilated and the right ventricle enlarged, the left ventricle and atrium appearing normal. The pulmonary trunk and the right and left main pulmonary arteries were small and peripheral pulmonary vascularity was decreased. There was a left aortic arch.

Cardiac catheterization showed equal systolic pressures in the right ventricle and in the aorta, which was thought to have been entered through a high ventricular septal defect. Arterial oxygen saturation was 65 per cent. The catheter could not be made to enter the pulmonary artery.

Biplane large roll film angiocardiograms *following* injection of contrast material into the right ventricle were considered preoperatively to indicate tetralogy of Fallot. In retrospect, *they showed that both the* large aorta and small pulmonary artery originated from the left ventricle, and were opacified simultaneously (Fig. 3).

At operation, on Nov. 11, 1964, the exterior of the heart seemed compatible with severe tetralogy *of Fallot*, but the aorta was more anterior and cephalad than usual in that malformation. The right ventricle was enlarged and hypertrophied and the coronary artery distribution normal. No thrill could be detected in the region of the left Blalock-Taussig anastomosis, which was not ligated. *Inspection* of the right ventricle through a vertical ventriculotomy during cardiopulmonary bypass showed a large ventricular septal defect, about 1.8 cm. in diameter which was slightly more cephalad and anterior than usual in the tetralogy of Fallot, being in the position characteristic of truncus arteriosus, or of pulmonary atresia with ventricular septal defect. The right atrioventricular valve was tricuspid *and the* right ventricular musculature was morphologically normal. The infundibulum of the right ventricle was extremely underdeveloped. *Neither* great artery

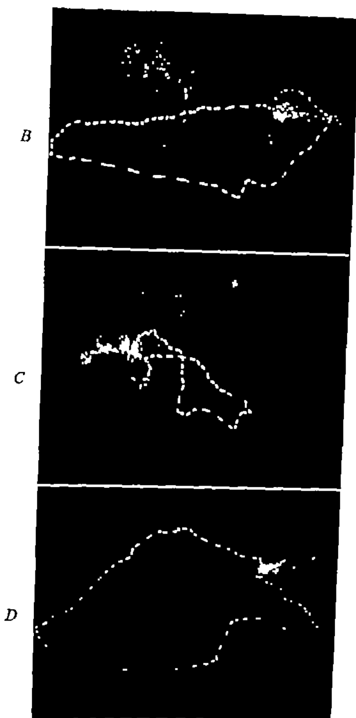


Fig 1 *B-D* Vectorcardiogram showing severe right ventricular hypertrophy as manifested by the 180 degree angle between the anteriorly oriented horizontal QRS loop and the posteriorly oriented T loop. The initial forces in these and in the electrocardiogram in Fig 1*A* suggest normally oriented septal depolarization. (1 mv = 2 cm.)

attached to the right ventricle. The aortic valve cusps could be seen through the ventricular septal defect. The pulmonary valve was tightly stenosed as viewed through a longitudinal incision in the pulmonary artery A probe passed retrograde through the pulmonary valve emerged *directly into* the left ventricle. The pulmonary artery thus arose entirely from the left ventricle. Direct inspection indicated that fibrous continuity existed between the anterior mitral leaflet and the aortic and pulmonary valves.

The ventricular septal defect was closed using a Dacron patch, leaving both great vessels emerging *from the left ventricle*. The stenotic pulmonary valve orifice was closed with sutures. Next, it was possible *to create the posterior half of a tunnel leading from the right ventricle* to the pulmonary artery by incising and undercutting the tissue in the area between the ventriculotomy and the longitudinal *incision in the pulmonary artery* An anterior half of *this tunnel* was constructed with a free graft of pericardium sutured to the edges of the incisions. Prior to closure of the sternotomy peak systolic pressure in the left ventricle was 95 mm. Hg, and in the sinus of the right ventricle 65 mm. Hg There was a gradient of 35 mm. Hg across the pericardial tunnel between the right ventricle and pulmonary artery

Early after the operation, the hemodynamic state was excellent. Severe pulmonary dysfunction necessitated assisted ventilation for a number of days. He was steadily improving until the seventh postoperative day when he suddenly developed left hemiparesis and semicoma. Presumably he suffered a cerebral thrombosis or embolism. This slowly improved and when discharged from the hospital on the forty ninth postoperative day motor function had returned almost to normal but some intellectual impairment persisted. Subsequent reports 15 months postoperatively indicate slow intellectual improvement with maintenance of excellent cardiac and pulmonary status.

Discussion

The case described is one of successful surgical correction of the malformation characterized by the following anatomic features. Both great arteries originated totally from the morphologic left ventricle The dilated aorta measured 1 9 times the pulmonary artery The two vessels were in a side by side interrelationship and the semilunar valves were at the same height. The pulmonary valve was severely stenotic. The right ventricle was enlarged with hypertrophy of the septal and free wall musculature. A subaortic ventricular septal defect was the only outlet of the right ventricle The infundibulum (conus) was very underdeveloped There was no interposition of the conus muscle (infundibulum) between the anterior leaflet of the mitral valve and the aortic and pulmonary semilunar valves. The heart chambers were normally interrelated in situs solitus

This malformation was recently interpreted by Van Praagh a differential conal growth hypothesis[6,7] In normal cardio-



Fig. 2. *A* and *B*. Frontal (*A*) and lateral (*B*) conventional chest roentgenograms show dilation of the right atrium and superior vena cava and enlargement of the right ventricle. The right and left main pulmonary arteries are small and peripheral pulmonary vascularity is decreased.

genesis the left-sided subpulmonary portion of the conus grows protruding the pulmonary valve anteriorly and superiorly in connection with the right ventricle. As the right-sided subaortic part of the conus does not develop the aortic valve remains posterior and inferior and related to the left ventricle In double-outlet left ventricle, right and left portions of the conus are absent or extremely hypoplastic. The valves of the great arteries remain posteriorly originating from the left ventricle in continuity with the anterior leaflet of the mitral valve.

The clinical and hemodynamic findings in our patient could not be distinguished preoperatively from those of severe tetralogy of Fallot. Retrospectively a careful examination of the angiocardiograms shows that both great arteries arose to the left of the ventricular septum. A left ventricular angiocardiogram would have led to the correct diagnosis by demonstrating the origin of both great arteries from the left ventricle and the continuity between mitral, aortic, and pulmonary valves without interposed conus. This emphasizes the value of a left ventricular angiocardiogram in the investigation of persons thought to have the severe form of tetralogy of Fallot to exclude double-outlet left ventricle or double-outlet right ventricle.

Intraventricular correction of one type of this malformation was accomplished by Sakakibara and associates. The case did not have pulmonary stenosis. The ventricular septal defect was large and subpulmonary permitting the intraventricular repair

In our case of double-outlet left ventricle with pulmonary stenosis, such a technique seemed precluded. The severe pulmonary stenosis and small pulmonary valve annulus required radical reconstruction. In this particular patient the procedure used worked well An obvious alternative was considered, namely use of a valved external conduit to establish continuity between right ventricle and pulmonary artery after closure of the ventricular septal defect and closure of the pulmonary valve.[8-11] The growth potential of the muscle forming the posterior wall of the tunnel used instead was thought to be advantageous in this small child.

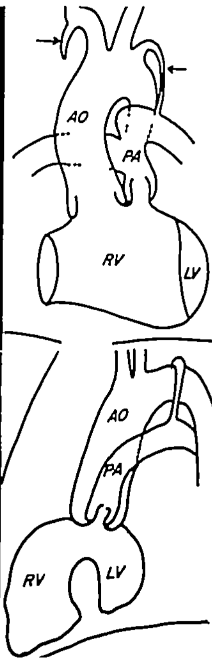
Summary

A case is reported of origin of both great arteries from the morphologic left ventricle, a rare malformation There was also a subaortic ventricular septal defect and severe pulmonary stenosis. The patient presented as having the severe form of tetralogy of Fallot. Surgical correction was made.

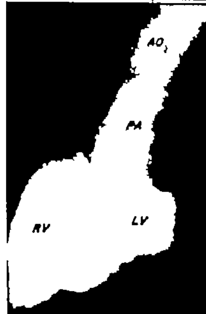
A B







D I



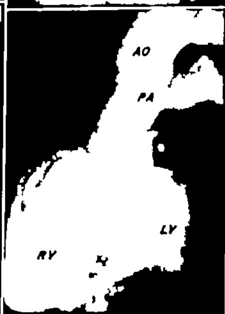


Fig 3 A F Right ventricular angiocardiograms (A and B are frontal projections, D and E are lateral projections, and C and F are sketches) The enlarged right ventricle (RV) has hypertrophied musculature and very hypoplasic infund'bulum (conus) and communicates w th a smaller left ventricle (LV) through a large ventricular septal defect. Both great arteries (AO = aorta P 1 = pulmonary artery) are located side by side and originate from the left ventricle. The semilunar valves are at the same horizontal plane. The pulmonary valve is markedly stenotic and the pulmonary valve ring narrow There is no conus (infundibular) musculature interposed between the anterior mitral leaflet and the aortic and pulmonary semilunar valves. The aortic valve is closer to the ventricular septal defect than is the pulmonary valve. The aortic arch is on the left. The left Blalock Taussig anastomosis is stenotic, and the right one is occluded.

REFERENCES

1 Fragoyannis, S. and Kardalinos, A.: Transposition of the great vessels, both arising from the left ventricle (juxtaposition of the pulmonary artery) Amer J Cardiol 10:601 1962.

2. Ruttenberg, H. D Anderson, R. C. Elliot L. P., and Edwards, J E. Origin of both great ... from the arterial ventricle: A complex with ventricular inversion, Brit. Heart J 26:631 1964.

3 Kiser J C., Ongley P A. Kirklin, J W Clarkson, P M., and McGoon, D C. Surgical treatment of dextrocardia with in version of ventricles and double-outlet right ventricle, J Thorac. Cardiovasc. Surg. 55:6, 1968.

4. Sakakibara, S. Takao, A. Arai, T Hashimoto,

A., and Nogl, M Both great vessels arising from the left ventricle, Bull. Heart Inst. Jap. p. 66, 1967
5. P ul, M. H., Muster A. J Sinha, S. N Cole, R. B., and Van Praagh, R.: Double-outlet left ventricle with an intact ventricular septum Clinical and autopsy diagnosis and developmental implications, Circulation 41:129 1970.
6. Van Praagh, R., and Van Praagh, S. Isolated ventricular inversion: A consideration of the morphogenesis, definition and diagnosis of nontransposed and transposed great arteries, Amer J Cardiol. 17:395 1966.
7. Paul, M H., Van Praagh, S., and Van Praagh, R. Transposition of the great arteries, Watson, H editor Paediatric cardiology St. Louis, 1968, The C. V Mosby Company p. 576.
8. Rastelli, G. C., Ongley P A., Davis, G D., and Kirklin, J W: Surgical repair for pulmonary al e atresia ith coronary-pulmonary artery fistula Report of a case, Mayo Clin. Proc. 40:532, 1965.
9. Ross, D. N and Sommerville, J: Correction of pulmonary tresia with homograft aortic valve, Lancet 2:1446, 1966.
10. Wallace, R. B., Rastelli, G. C., Ongley P A. Titus, J L., and McGoon, D C. Complete repair of truncus arteriosus defects, J Thorac. Cardiovasc. Surg. 57:95, 1969
11. Rastelli, G. C., Wallace, R. B., and Ongley P A. Complete repair of transposition of the great arteries with pulmonary stenosis, Circulation 39:83, 1969

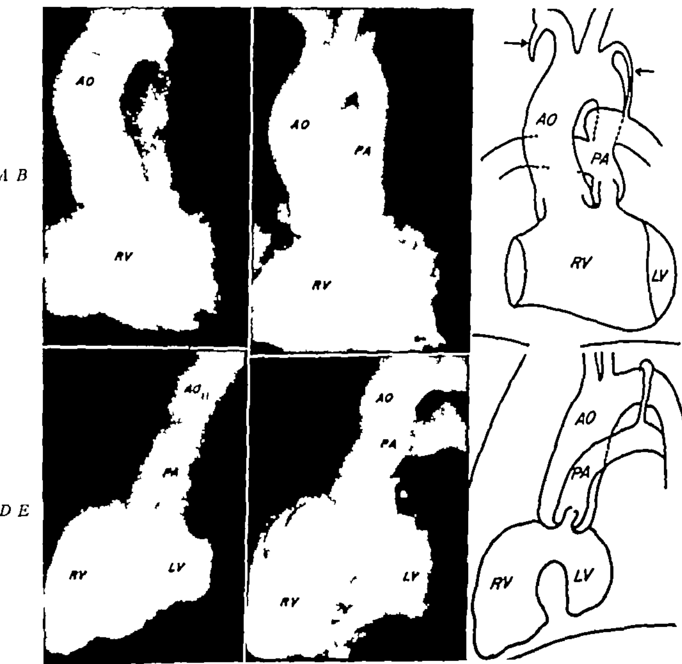


Fig 3 A-F Right ventricular angiocardiograms (A and B are frontal projections, D and E are lateral projections, and C and F are sketches) The enlarged right ventricle (RV) has hypertrophied musculature and very hypoplastic infundibulum (conus) and communicates with a smaller left ventricle (LV) through a large ventricular septal defect. Both great arteries (AO = aorta PA = pulmonary artery) are located side by side and originate from the left ventricle. The semilunar valves are at the same horizontal plane. The pulmonary valve is markedly stenotic and the pulmonary valve ring narrow There is no conus (infundibular) musculature interposed between the anterior mitral leaflet and the aortic and pulmonary semilunar valves. The aortic valve is closer to the ventricular septal defect than is the pulmonary valve. The aortic arch is on the left. The left Blalock Taussig anastomosis is stenotic, and the right one is occluded.

REFERENCES

1. Fragoyannis, S. and Kardalinos, A. Transposition of the great vessels, both arising from the left ventricle (juxtaposition of the pulmonary artery) Amer J Cardiol. 10:601 1962.
2. Ruttenberg H. D Anderson, R. C. Elliot, L. P., and Edwards, J E.: Origin of both great [illegible] ventricle: A complex with ventricular inversion, Brit. Heart J 26:631 1964
3. Kiser J C. Ongley P A., Kirklin J W Clarkson, P M and McGoon, D C.: Surgical treatment of dextrocardia with inversion of ventricles and double-outlet right ventricle, J Thorac. Cardiovasc. Surg. 55:6, 1968.
4. Sakakibara, S., Takao, A., Arai, T Hashimoto,

Shock associated with sepsis is most often seen with gram-negative bacteremia but can also be seen in some patients with gram-positive bacteremia.[15] Endotoxin appears to be the responsible shock-producing factor in gram-negative and occasionally in gram-positive bacteremia, especially that due to group A hemolytic streptococci.[16] In gram-negative sepsis the shock state is usually preceded several hours by high temperatures (104 to 106° F.) and chills in a patient with a predisposing condition such as an indwelling urinary catheter, recent manipulation or surgery of the genitourinary or gastrointestinal tract, peritonitis, chronic or acute urinary tract infection, and chronic or acute debilitative diseases (cirrhosis, blood dyscrasias, neoplasms, renal disease, diabetes, and old age).[17] Initially the white blood cell count may be below 5,000 per cubic millimeter but in time may increase to 25,000 to 30,000 per cubic millimeter. There may be marked dehydration, electrolyte derangement, and acidosis, or none of these, depending upon the underlying disorder and the stage of shock.

In a small percentage of patients—much less than previously thought—the warm shock picture predominates and is characterized by hypotension, warm pink skin, little alteration of sensorium (except delirium which may be associated with extremely high temperatures), and adequate urine output. This appears to be a rather rapid and transient phase which progresses into the more commonly seen vasoconstrictive shock manifested by hypotension, pallor, peripheral cyanosis, cool clammy skin, tachycardia, marked derangement of the sensorium, rapid and irregular respiration, and oliguria or anuria.[18] Not infrequently vasoconstrictive shock may be present in a patient with a normal blood pressure. More will be said about this later.

Worthy of emphasis are certain features that are more characteristic of gram-negative sepsis than other types of shock. Hyperventilation[11,17] and tachypnea have been regularly observed both experimentally and clinically due apparently to a direct effect of endotoxin on the respiratory center. Often the excessive ventilatory effort leads to a marked drop in the pCO_2 and respiratory alkalosis early in the course of endotoxin shock, mimicking pulmonary embolism which is sometimes seen in the same setting. As shock progresses the respiratory alkalosis gradually gives way to a metabolic acidosis which may be distinguished only by the change from a high to a lower arterial blood pH. Peripheral cyanosis appears early in the course of gram-negative shock and eventually becomes more profound as shock worsens. The degree and extent of cyanosis seems to be disproportionate to the measured blood pressure and often more pronounced than the peripheral cyanosis associated with other types of shock. It apparently reflects intense peripheral vasoconstriction caused by excessive catecholamines and perhaps other vasoactive substances.[11,17,18,21]

We have noted that one of the earlier signs of circulatory embarrassment is a cool and/or cyanotic knee. This has been noted in a number of patients who subsequently developed the full-blown picture of shock irrespective of whether sepsis, hemorrhage, or cardiogenic factors were responsible. The cyanosis may be barely perceptible and splotchy but is usually accompanied by a reduced temperature over the patella. Often this occurs before the hands or feet develop cyanosis, before the urine output begins to diminish and not infrequently before the decline of the brachial blood pressure. The observation of the knees has provided a useful tool in the early recognition of circulatory insufficiency of any etiology and has served as a guide in following response to therapy. Joly and Weil[22] recently reported the use of a thermistor to detect early changes in blood flow in the toes of patients in shock, but obviously such a device is primarily a research tool and may be inaccessible to physicians serving outside of large medical centers. The gross clinical observation of the knee, though less sophisticated, may provide a reasonable substitute in determining the status of peripheral perfusion of a patient in shock. Why the skin over the patella lends itself to early detection of such changes is not known but it may be that dermal thickness of this area is reduced which, upon stretching produced by even slight knee flexion, makes ab-

Pathophysiology of gram-negative shock

*James H. Christy, M.D.**
Atlanta, Ga.

Gram-negative bacteremia has long been recognized, but it was not until 1951 that acknowledgement was made of the specific shock syndrome that can occur in patients with gram-negative sepsis.[1,2] Since then large series of patients with gram-negative bacteremia and shock have been reported[3-10] and the mortality rate has remained appallingly high despite recent advances in antibiotic, fluid, and shock therapy. Undoubtedly, such dismal therapeutic results have been due in part to our poor understanding of the pathogenesis, hemodynamic, and biochemical events of endotoxin shock. The high mortality rate together with the five- to eightfold increase in the incidence of gram-negative sepsis over the past 20 years[11] have created an urgent demand for better understanding of the pathophysiology of and more effective therapy for gram-negative shock.

Recently, gallant attempts to elucidate some of the pathophysiologic mechanisms have been made, and the importance of the microcirculation in this and other forms of shock has been emphasized.[12,13] Certain investigators have stressed the necessity of restoring and maintaining the integrity of the microcirculation through the use of massive fluid administration,[13] plasma expanders,[13,14] beta-adrenergic stimulators,[10,14,15] alpha-adrenergic blockade,[10] and more recently massive corticosteroids.[7,9,12,15,16] An inherent problem in such investigative work, however, has been the necessity of using experimental animals for the shock model, and the pitfalls of extrapolating these results to the human are well known.

It is the purpose of this communication to review briefly the pathophysiology of gram-negative shock, hoping to provide at least a superficial understanding of those circulatory and metabolic derangements that are potentially reversible through a more physiologic therapeutic approach.

Clinical gram-negative shock

The constellation of hypotension, weak thready pulses, cool clammy skin, tachycardia, alteration of respiration and sensorium, peripheral cyanosis, and oliguria is well known and universally recognized as the clinical expression of shock or circulatory insufficiency. The hemodynamic basis for this picture is the failure to supply oxygenated blood in a volume and under a pressure sufficient to maintain adequate perfusion of vital organs.[17] The same syndrome may be seen in any shock state irrespective of etiology: (1) primary failure of the cardiac pump (myocardial infarction, severe congestive heart failure, arrhythmias), (2) hemorrhage and fluid loss, (3) anaphylaxis, (4) endocrine failure, and (5) sepsis.[18,19]

From the Department of Medicine, Emory University School of Medicine, and Emory University Hospital, Atlanta, Ga.
Reprint requests to: 1365 Clifton Road, N.E., Atlanta, Ga. 30322.
*Assistant Professor of Medicine.

Shock associated with sepsis is most often seen with gram-negative bacteremia but can also be seen in some patients with gram-positive bacteremia.[23] Endotoxin appears to be the responsible shock producing factor in gram-negative and occasionally in gram-positive bacteremia especially that due to group A hemolytic streptococci.[24] In gram negative sepsis the shock state is usually preceded several hours by high temperatures (104 to 106° F) and chills in a patient with a predisposing condition such as an indwelling urinary catheter recent manipulation or surgery of the genitourinary or gastrointestinal tract peritonitis, chronic or acute urinary tract infection, and chronic or acute debilitative diseases (cirrhosis, blood dyscrasias, neoplasms, renal disease, diabetes, and old age).[22] Initially the white blood cell count may be below 5,000 per cubic millimeter but in time may increase to 25 000 to 30 000 per cubic millimeter. There may be marked dehydration electrolyte derangement and acidosis, or none of these depending upon the underlying disorder and the stage of shock.

In a small percentage of patients—much less than previously thought—the warm shock picture predominates and is characterized by hypotension, warm pink skin little alteration of sensorium (except delirium which may be associated with extremely high temperatures) and adequate urine output. This appears to be a rather rapid and transient phase which progresses into the more commonly seen vasoconstrictive shock manifested by hypotension pallor peripheral cyanosis, cool clammy skin tachycardia, marked derangement of the sensorium rapid and irregular respiration, and oliguria or anuria.[24] Not infrequently vasoconstrictive shock may be present in a patient with a normal blood pressure. More will be said about this later.

Worthy of emphasis are certain features that are more characteristic of gram-negative sepsis than other types of shock. Hyperventilation[11,27] and tachypnea have been regularly observed both experimentally and clinically due apparently to a direct effect of endotoxin on the respiratory center. Often the excessive ventilatory effort leads to a marked drop in the pCO and respiratory alkalosis early in the course of endotoxin shock mimicking pulmonary embolism which is sometimes seen in the same setting. As shock progresses the respiratory alkalosis gradually gives way to a metabolic acidosis which may be distinguished only by the change from a high to a lower arterial blood pH. Peripheral cyanosis appears early in the course of gram negative shock and eventually becomes more profound as shock worsens. The degree and extent of cyanosis seems to be disproportionate to the measured blood pressure and often more pronounced than the peripheral cyanosis associated with other types of shock. It apparently reflects intense peripheral vasoconstriction caused by excessive catecholamines and perhaps other vasoactive substances.[11,27,28,31]

We have noted that one of the earlier signs of circulatory embarrassment is a cool and/or cyanotic knee. This has been noted in a number of patients who subsequently developed the full-blown picture of shock irrespective of whether sepsis, hemorrhage, or cardiogenic factors were responsible. The cyanosis may be barely perceptible and splotchy but is usually accompanied by a reduced temperature over the patella. Often this occurs before the hands or feet develop cyanosis, before the urine output begins to diminish and not infrequently before the decline of the brachial blood pressure. The observation of the knees has provided a useful tool in the early recognition of circulatory insufficiency of any etiology and has served as a guide in following response to therapy. Joly and Weil[32] recently reported the use of a thermistor to detect early changes in blood flow in the toes of patients in shock, but obviously such a device is primarily a research tool and may be inaccessible to physicians serving outside of large medical centers. The gross clinical observation of the knee, though less sophisticated may provide a reasonable substitute in determining the status of peripheral perfusion of a patient in shock. Why the skin over the patella lends itself to early detection of such changes is not known but it may be that dermal thickness of this area is reduced which upon stretching produced by even slight knee flexion makes ab-

normal events of the circulation more readily perceptible

Experimental gram-negative shock

Endotoxin the substance believed to be the shock producing factor in infections due to gram negative organisms is a lipo-protein-carbohydrate complex found in the O somatic antigen present in the bacterial cell wall Studies by Spink[27] indicate that endotoxin obtained from different species of gram negative bacilli differ in potency and probably chemical composition Most of the experimental work concerning gram negative shock has been done in various species of laboratory animals and has consisted primarily of observations on the effects of a given quantity of standardly prepared endotoxin injected into the animal Though dogs cats mice rabbits and monkeys have been used experimentally[13,27,33,34] the precise features of the clinical entity of gram negative shock in man have not been completely produced in any given species of animal and thus has raised serious questions as to whether experimental endotoxic shock is relevant to clinical endotoxic shock in man Nevertheless since the potential dangers of injecting endotoxin into human volunteers would be prohibitive the laboratory animal must remain the experimental model for the study of endotoxin shock There have been reports of gram negative shock following the transfusion of contaminated blood which to date is the nearest human counterpart to experimental septic shock[35,37]

Endotoxin injected into the dog results in an immediate decrease in the systemic blood pressure accompanied by a rise in the portal vein pressure. Simultaneously there is an increase in the histamine concentration of hepatic vein blood and marked vasoconstriction of the portal veins.[27] Later there is partial recovery of the blood pressure followed by a secondary phase of hypotension that is accompanied by a progressive decrease in the cardiac output In creased catecholamine activity decreased peripheral blood flow decreased plasma volume oliguria and eventually death several hours after the injection. Autopsy findings are similar to those in animals which have died of hemorrhagic shock. The principal damage is in the small intestine which shows extensive pooling of blood and hemorrhagic necrosis of the mucosa. Less severe hemorrhagic congestion is noted in the lungs, liver and kidneys.[33] In the cat and monkey endotoxin results in a significant decrease in venous return and decreased cardiac output but of much less magnitude than in the dog In the cat, rabbit and monkey the site of pooling is primarily in the pulmonary bed[27,34,38-40] Vaughn and associates[34] noted pooling of blood and pulmonary congestion normal central venous pressure decreased cardiac output and shock in monkeys following the infusion of endotoxin Autopsy findings were remarkably similar to those of patients who had died of bacteremic shock and it was hypothesized that the lungs may be the primary site of pooling of blood in primates subjected to endotoxinemia.

That endotoxin is a potent shock producing agent is undisputed but how it results in profound hemodynamic alterations is still obscure Several investigators have shown that endotoxin does not act directly upon the vessel wall but its activity seems to be mediated through a heat labile serum factor forming a proteolytic substance which then acts upon elements or other cells in the blood to release certain vasoactive substances including histamine[27] serotonin[41] acetylcholine,[42] bradykinin[43,44] and catecholamines.[13,27,33] Some studies have shown that varying degrees of protection can be offered to the animal by antihistamines and antiserotonin[44] or antiproteolytic agents such as epsilon amino caproic acid[44] but the results have not been convincing enough to warrant their use in clinical practice. The role of catecholamines is not clear in the early phase of shock but norepinephrine appears to play a major role in a later phase[13,27] perhaps as a result of progressive diminution of cardiac output There is also evidence that endotoxin in some way sensitizes and accentuates the vasoconstrictive response to epinephrine.[13]

Immune mechanisms have been implicated in the pathogenesis of gram negative shock but their role is even more obscure than that of the factors discussed above. Partial evidence for antigen-anti

Pathophysiology of Gram Negative Shock

ENDOTOXIN

BLOOD

ACTIVATION OF
? PROTEOLYTIC ENZYME
? ANTIGEN ANTIBODY REACTION
UNDEFINED MECHANISMS

HISTAMINE
SEROTONIN
BRADYKININ
OTHER VASOACTIVE SUBSTANCES

POOLING OF BLOOD

VENOUS RETURN

CARDIAC OUTPUT

CELLULAR HYPOXIA

Acidosis

DISRUPTION LYSOSOMES

LYSOZYMES

CELL LYSIS

PROPAGATION OF TISSUE INJURY

TIME

IRREVERSIBILITY

Capillary Congestion

Sensitivity to Catecholamines

VENULAR CONSTRICTION

TISSUE ACIDOSIS

Fig. 1 Schematic representation summarizing the pathophysiology of gram-negative shock.

body phenomena has been the observation of decreased serum complement in rabbits after endotoxin injection.[14] Further support comes from the observations of Abernathy and associates[13, 16] that (1) resistance of mice to brucella endotoxin is decreased after the establishment of chronic brucella infection and (2) man is markedly sensitive to brucella endotoxin following recovery from brucellosis.

Disseminated intravascular coagulation. Hardaway[13, 18, 21] has championed the concept of disseminated intravascular coagulation (DIC) as a major factor in the evolution of irreversible shock whether it be due to endotoxin, hemorrhage or cardiogenic factors. In a recent study of patients referred to the Shock Unit at Walter Reed Hospital for treatment of prolonged refractory shock, Hardaway and co-workers[13] noted deficiency of multiple blood-clotting factors in all patients including 6 with

gram negative shock. These coagulation defects were believed to reflect consumption of clotting factors by disseminated intravascular coagulation Corrigan and associates[12] reported similar findings on a group of pediatric patients with septicemia All 11 patients with septic shock showed coagulation defects compatible with diffuse intravascular coagulation whereas only 6 of 25 normotensive patients with sepsis showed defects in the clotting mechanism McKay and co-workers[13] observed typical pathologic findings of the generalized Schwartzman phenomenon in several patients who developed shock in the course of septic abortion and concluded that endotoxinemia produces many of the associated hemodynamic alterations of endotoxin shock as a result of disseminated intravascular coagulation

Whether disseminated intravascular coagulation is a cause or an effect of the profound shock of patients with gram negative sepsis is problematical but its effect would be to impede perfusion of the capillary beds resulting in tissue hypoxia and lactic acidosis as well as reduction of venous return to the heart with further decrease in cardiac output and related sequelae A serious problem associated with DIC is localized or generalized hemorrhagic diathesis due to the consumption of clotting factors[12,41] This is not seen in every case however

Role of the microcirculation Some of the most exciting work regarding the pathogenesis and treatment of experimental endotoxin shock has been reported by Lillehei and associates[15] These investigators focused attention to the function of the microcirculation in shock of various etiologies. In dogs they demonstrated that whether shock is of hemorrhagic cardiac or septic origin it is the functional status of the microcirculation that determines whether the animal survives or dies. In the initial stage of shock the precapillary arterioles and postcapillary venules undergo spasm in response to catecholamine stimulation of alpha receptors which results in ischemic capillary beds of the splanchnic circulation This is termed the phase of ischemic anoxia and reversibility of shock can be achieved if the original cause of shock is corrected If shock continues unabated the precapillary vessel tone relaxes as a result of refractoriness of the arteriolar receptors to catecholamine stimulation This recalcitrance of the arteriolar sphincters is probably a consequence of local lactic acidosis developing after prolonged ischemia The postcapillary venous sphincters are more resistant to the effects of tissue acidosis probably because they operate normally in a lower pH range. As a result the capillary beds become congested giving rise to an egress of fluid out of the capillaries into the interstitial tissues where it is lost from the circulation. This is referred to as the stagnant anoxia phase. The combined factors of trapping of blood in the capillary beds, fluid loss into the tissues, and continued vasoconstriction under the influence of high catecholamine levels constitute an irreversible phase of shock and tissue perfusion becomes insufficient to sustain life It should be emphasized that whether the experimental shock state is induced by endotoxin hemorrhage coronary occlusion or prolonged infusion of epinephrine the hemodynamic events of the microcirculation appear to be identical[15] inferring certain therapeutic implications.

There has been some question as to whether the physiologic events of endotoxin shock in the dog and other animals are applicable to gram negative shock in humans. The detailed studies of Udhoji and colleagues[16] on the physiologic alterations of patients with bacteremic shock have dispelled some of the doubts expressed earlier They found that these patients characteristically had a low cardiac output more than twofold increase in the peripheral vascular resistance and normal or low central blood volumes and venous pressures. These findings were compatible with the view that pooling of blood occurs in the venous side of the circuit and that vasomotor dilatation or collapse is not the primary mechanism in this type of shock Localization of the venous pooling remains unclear in the human however

Effects of endotoxin on the myocardium For years the belief has been commonly held that the myocardium is remarkably resistant in endotoxin shock and that

ilure of the heart occurs only in the terminal phase of shock when coronary blood flow is diminished hence cardiac depression has not been considered to be a primary cause of circulatory failure in endotoxin shock. Recently however Solis and Downing[14] demonstrated in cats a definite deleterious effect of endotoxin on myocardial function. By controlling hemodynamic variables such as cardiac input, heart rate, and aortic pressure, and plotting stroke volume against left ventricular end-diastolic pressure at periodic intervals following endotoxin injection, they showed progressive deterioration of left ventricular function curves over a period of two hours. They were able to overcome this effect of endotoxin with both isoproterenol and angiotensin II infusions. Response to angiotensin was of particular interest because this drug exhibits an inotropic effect only in hearts manifesting markedly decreased contractility therefore, this could be considered additional, though indirect, evidence that endotoxin has an adverse effect on cardiac contractility If these observations are valid, the mechanism by which endotoxin exerts this effect is unclear but does not seem to be related to histamine and serotonin release, both of which were noted to have an inotropic effect on the same preparation.

A point against the theory that endotoxin affects myocardial contractility in human endotoxin shock is the failure to demonstrate elevated *central venous pressure* in a number of these patients. Solis and Downing[14] reason, however that this observation in the presence of a cardiac output that is 25 per cent of normal does not preclude the possibility that the central venous pressure would be substantially elevated if the myocardium were forced to perform a normal work load. This point remains debatable but may be a more important factor in the pathophysiology of gram negative shock than previously thought.

Alterations in lysosomes

Recently attention has been directed to the role of lysosome alteration in traumatic injury and shock.[11-14] It is well known that these organelles contain precursors of certain vasoactive peptides as well as a number of cytolytic enzymes, proteases, and phosphatases. Disruption of the lysosome releases these toxic substances into the cytoplasm of the parent cell as well as into the circulation resulting in widespread cellular and tissue injury Lysosome enzymes (lysozymes) are most active in the acid pH range thus it might be expected that the cellular hypoxia occurring in protracted shock and the attendant metabolic acidosis would activate these enzymes.

In a series of elegant experiments, Janoff and associates[14] demonstrated increased release of hepatic lysosome enzymes (cathepsins, acid phosphatase, and beta glucuronidase) into the supernate of centrifuged large granule fractions of liver and into the circulation of mice and rabbits following rotational trauma or endotoxin induced shock. Conversely pretreatment of the animals with cortisone or development of tolerance to trauma injury by prior conditioning reduced or prevented the increase in plasma acid phosphatase and beta glucuronidase normally resulting from endotoxin injection and trauma. Similarly there was reduced release of these substances into the supernate of centrifuged large granule fractions of liver It would thus seem that in a state of ineffectively treated shock of endotoxic origin lysosome disruption and lysozyme activation would propagate cell and tissue injury and might well contribute to irreversibility of shock and a lethal outcome.

Biochemical events

A detailed discussion of cellular biochemistry in shock is not within the province of this paper but a nice summary of the problem has been offered by Schumer and Sperling[4] They consider shock of whatever etiology to be a molecular disease in which the metabolic derangements evolve about anaerobic glucose metabolism resulting in increased production of lactic acid, amino acids, fatty acids, and phosphoric acids. The metabolic acidemia produces lysosome membrane disruption as mentioned previously Decreased production of the energy component, adenosine triphosphate, results in deranged protein synthesis and cell membrane pump

function which in turn reduce the ability of the organism to combat shock.

Conclusion

It is difficult to define the physiologic biochemical and pathologic mechanisms for gram negative shock even in a single species of laboratory animal In man the problem is compounded by a diversity of diseases, organisms rapidly changing clinical events and other variables which make it virtually impossible to carry out meaningful controlled studies of the mechanisms and treatment of shock Nonetheless, we are faced with the problem of gram negative shock in all areas of medicine and must have some broad concept of the pathophysiology of endotoxin shock in order to develop a more intelligent therapeutic approach to it. In Fig 1 a composite scheme summarizes some highlights of the pathophysiology of gram negative shock presented in the foregoing discussion It is acknowledged that many of the steps in the scheme are based upon animal experimentation and may be more convenient than relevant to human gram negative shock but the author has found it very useful as a base for a more sound physiologic approach to the therapy of this problem with gratifying results ••

REFERENCES

1 Walsbren, B A Bacteremia due to gram negative bacilli other than Salmonella Arch. Intern. Med. 88:467 1951
2. Waisbren B A. Gram negative shock and endotoxin shock Amer J Med. 36:819 1964
3 Weil, M H and Spink, W W The shock syndrome associated with bacteremia due to gram negative bacilli, Arch. Intern. Med 101:184 1958.
4 McHenry M C. Martin W J and Wellman W E.: Bacteremia due to gram negative bacilli Review of 113 cases encountered in 5 year period 1955 through 1959 Ann. Intern. Med. 56:207 1962.
5. McCabe, W R and Jackson G G Gram negative bacteremia. I Etiology and ecology II Clinical laboratory and therapeutic observations, Arch. Intern. Med. 110:847 1962
6. Shubin H and Weil M H. Bacterial shock A serious complication in urological practice, J.A.M.A. 185:850, 1963.
7 Weil, M. H., Shubin, H. and Biddle, M. Shock caused by gram negative microorganisms: Analysis of 169 cases, Ann. Intern. Med. 60:384, 1964.
8. Hodgin, U G. and Sanford J P Gram negative rod bacteremia. An analysis of 100 patients, Amer J Med. 39:952 1965.
9 Melnick I., and Litvak, A. Gram negative bacteremia: An evaluation of fifty-nine cases during 1963 J Urol. 96:257 1966.
10. MacLean L. D., Mulligan, W G., McLean, A. P H and Duff J H Patterns of septic shock in man A detailed study of 56 patients, Ann. Surg 166:543 1967
11 Rogers, D E Koenig G. and Holmes, K K: The problem of gram negative bacteremia and its management Southern Med. J 58:1391 1965
12. Lillehei, R. C. Longerbeam, J K., Bloch, J H., and Manax, W G. Nature of irreversible shock Experimental and clinical observations, Ann. Surg 160:682 1964
13. Hardaway R. M James, P M Anderson, R. W., Bredenberg C. E., and West, R. L. Intensive study and treatment of shock in man, J.A.M.A. 199:779 1967
14. MacLean, L. D Duff J H., Scott, H. M and Peretz, D I: Treatment of shock in man based on hemodynamic diagnosis, Surg Gynec. Obstet. 120:1 1965.
15 Krasnow N Rolett, E. L., Yurchak, P M., Hood, W B Jr., and Gorlin, R. Isoproterenol and cardiovascular performance, Amer J Med. 37:514 1964
16. Kardos, G G.: Isoproterenol in the treatment of shock due to bacteremia with gram negative pathogens, New Eng J Med. 274:868, 1966.
17 Weil M H., and Shubin, H Isoproterenol for the treatment of circulatory shock, Ann. Intern. Med. 0:638, 1969
18. McCannell, K. L. McNay J L., Meyer M. B., and Goldberg, L. I. Dopamine in the treatment of hypotension and shock, New Eng J Med. 275:1389 1966.
19 Wilson, R. F Jablonski D. V., and Thal, A. P: Usage of dibenzyline in clinical shock, Surgery 56:172, 1964.
20. Lillehei, R. C. Longerbeam, J K. Bloch, J H and Manax, W G.: Modern treatment of shock based on physiologic principles, Clin. Pharmacol. Ther 5:63 1964.
21 Melby J C. Corticosteroids in shock in man and animals, New Physician 13:426, 1964.
22. Sambhi M P Weil, M. H., and Udhoji, V N Acute pharmacodynamic effects of glucocorticoids on cardiac output and related hemodynamic changes in normal patients and patients in shock, Circulation 31:523, 1965.
23. Spink, W W Bacteremic shock, Hosp. Med. 2:24 1966.
24 Cavanagh D Clark, P J and McLeod, A. G. W Septic shock of endotoxin type, Amer J Obst. Gynec. 102:13 1968.
25. Wilson, R. F., and Fisher R. R. The hemodynamic effects of massive steroids in clinical shock, Surg Gynec. Obstet. 127:769 1968.
26. Blair E., Wise, A. and Mackay A. G. Gram negative bacteremic shock Mechanisms and management, J.A.M.A. 207:333 1969
27 Spink, W W Endotoxin shock, Ann. Intern. Med. 57:538, 1962.

28. Weil, M. H., and Shubin, H. S. Diagnosis and treatment of shock, Baltimore, 1967 The Williams & Wilkins Company
29. Stetson, C. A. The endotoxic properties of lysates of group A hemolytic streptococci, J Exp. Med. 104:921 1956.
30. Udhoji, V N., Weil, M. H., Sambhi, M P and Rosoff L. Hemodynamic studies on clinical shock associated with infection. Amer J Med. 34:461, 1963.
31. Zweifach, B. W Nagler A. L., and Thomas, L.: The role of epinephrine in the reactions produced by the endotoxins of gram-negative bacteria. II. The changes produced by endotoxin in the vascular reactivity to epinephrine in the rat mesoappendix and the isolated perfused rabbit ear J Exp. Med. 104:881 1956.
32. Joly H. R., and Weil, M. H. Temperature of the great toe as an indication of the severity of shock, Circulation 39 131 1969.
33. Spink, W W. The pathogenesis and management of shock due to infection, Arch. Intern. Med. 106:433 1960.
34. Vaughn, D L., Gunter C. A and Stookey J L. Shock in primates, Surg. Gynec. Obstet. 126 1309 1968.
35. Borden, C. W and Hall, W H. Fatal transfusion reactions from massive bacterial contamination of blood, New Eng J Med. 245 760, 1951.
36. Stevens, A. R. Legg, J S., Henry B S Dille, J M Kirby W M and Finch, C. A Fatal transfusion reactions from contamination of stored blood by cold growing bacteria, Ann. Intern. Med. 39 1228, 1953.
37. Braude, A. I Siemienski, J Williams, D and Sanford, J P Overwhelming bacteremic shock produced by gram negative bacilli A report of four cases with one recovery Univ Mich Med. Bull. 19:23 1953
38. Kuida, H., Gilbert, R. P Hinshaw L. B., Brunson, J G., and Visscher M. B. Species differences in effect of gram negative endotoxin on circulation, Amer J Physiol. 200 1197 1961.
39. Weil, M H The animal model and the human patient in bacterial shock, in Landy M and Braun, W editors. Bacterial endotoxins. Proceedings of symposium held at the Institute of Microbiology of Rutgers, the State University New Brunswick, 1964 p 187
40. Robins, J Views and reviews: Modern concepts in the management of shock, Obstet. Gynec. 28 130, 1966.
41. Davis, R. B., Meeker W R., J and Bailey W L. Serotonin release by bacterial endotoxin, Proc. Soc. Exp Biol. Med. 108:774 1961.
42. Thal, A. P and Wilson, R. F Shock, in Current problems in surgery Chicago, 1965, Year Book Medical Publishers, Inc.
43. Thal, A. P and Sardesai, V M. Shock and the circulating polypeptides, Amer J Surg. 110:308, 1965.
44. Gilbert, R. P: Effect of antihistamine and antiserotonin drugs on vascular responses to E. coli endotoxin in the cat, Proc. Soc. Exp. Biol. Med. 100:364 1959
45. Spink, W W and Vick, J A. Endotoxin shock and the coagulation mechanism Modification of shock with epsilon aminocaproic acid, Proc. Soc. Exp. Biol. Med. 106:242, 1961
46. Gilbert, V E., and Braude, A. L Reduction of serum complement by endotoxin in vivo, Fed. Proc. 21 17 1962.
47. Abernathy R. S., Bradley G. M and Spink, W W Increased susceptibility of mice with brucellosis to bacterial endotoxins, J Immunol. 81:271 1958.
48. Abernathy R. S., and Spink, W W Studies with brucella endotoxin in humans. The significance of susceptibility to endotoxin in the pathogenesis of brucellosis, J Clin. Invest. 37:219 1958.
49. Hardaway R. M Husni, E. A., Geever E. F., Noyes, H. E., and Burns, J U.: Endotoxin shock A manifestation of intravascular coagulation, Ann. Surg. 154 791 1961.
50. Hardaway R. M. Microcoagulation in shock, Amer J Surg. 110:298, 1965.
51. Hardaway R. M. Syndromes of disseminated intravascular coagulation: With special reference to shock and hemorrhage, Springfield, Ill., 1966, Charles C Thomas, Publisher p. 290.
52. Corrigan, J J Ray W L., and May N., Changes in the blood coagulation system associated with septicemia, New Eng. J Med. 279:851, 1968.
53. McKay D G., Jewett, J F and Reid, D E. Endotoxin shock and the generalized Schwartzman reaction in pregnancy Amer J Obstet. Gynec. 78:546, 1959
54. Solis, R. J and Downing, S. E. Effects of E. coli endotoxin on ventricular performance, Amer J Physiol. 211:307 1966.
55. Weissman, G., and Thomas, L. Studies on lysosomes. The effects of endotoxin, endotoxin tolerance, and cortisone on the release of acid hydrolases from granular fraction of rabbit liver J Exp. Med. 116:433, 1962.
56. Janoff A., Weissman, G., Zweifach, B. W and Thomas, L., Pathogenesis of experimental shock. IV Studies on lysosomes in normal and tolerant animals subjected to lethal trauma and endotoxinemia, J Exp. Med. 116:451 1962.
57. Janoff A. I Hershey S. G., editor Shock, Boston, 1964, Little, Brown & Company p. 93.
58. Weissman, G. Lysosomes, New Eng. J Med. 273 1143 1965.
59. Shumer W and Sperling, R. Shock and its effect on the cell, J.A.M.A. 205:215, 1968.
60. Submitted for publication.

function which in turn reduce the ability of the organism to combat shock

Conclusion

It is difficult to define the physiologic biochemical and pathologic mechanisms for gram negative shock even in a single species of laboratory animal In man the problem is compounded by a diversity of diseases, organisms rapidly changing clinical events and other variables which make it virtually impossible to carry out meaningful controlled studies of the mechanisms and treatment of shock Nonetheless, we are faced with the problem of gram negative shock in all areas of medicine and must have some broad concept of the pathophysiology of endotoxin shock in order to develop a more intelligent therapeutic approach to it In Fig 1 a composite scheme summarizes some highlights of the pathophysiology of gram negative shock presented in the foregoing discussion It is acknowledged that many of the steps in the scheme are based upon animal experimentation and may be more convenient than relevant to human gram negative shock but the author has found it very useful as a base for a more sound physiologic approach to the therapy of this problem with gratifying results [44]

REFERENCES

1 Waisbren, B A. Bacteremia due to gram negative bacilli other than Salmonella Arch Intern. Med. 88:467 1951
2 Waisbren B. A. Gram negative shock and endotoxin shock Amer J Med. 36:819 1964
3. Weil M H and Spink W W The shock syndrome associated with bacteremia due to gram negative bacilli, Arch. Intern. Med. 101:184 1958.
4. McHenry M C. Martin W J and Wellman W E.: Bacteremia due to gram negative bacilli Review of 113 cases encountered in 5 year period 1955 through 1959 Ann. Intern. Med 56:207 1962.
5 McCabe W R. and Jackson, G G Gram negative bacteremia. I Etiology and ecology II Clinical laboratory and therapeutic observations, Arch. Intern. Med. 110:847 1962
6. Shubin H and Weil M H : Bacterial shock: A serious complication in urological practice J.A.M.A. 185:850 1963
7 Weil M H. Shubin, H and Biddle, M : Shock caused by gram negative microorganisms: Analysis of 169 cases, Ann. Intern. Med. 60:384, 1964
8. Hodgin, U G. and Sanford, J P Gram negative rod bacteremia: An analysis of 100 patients, Amer J Med. 39:952, 1965.
9 Melnick I and Litvak, A. Gram negative bacteremia An evaluation of fifty nine cases during 1963 J Urol. 96:257 1966.
10. MacLean L. D., Mulligan W G., McLean, A. P H., and Duff J H Patterns of septic shock in man A detailed study of 56 patients, Ann. Surg 166:543 1967
11 Rogers, D E. Koenig G. and Holmes, K K: The problem of gram negative bacteremia and its management Southern Med. J 58:1391, 1965.
12. Lillehei, R. C. Longerbeam J K., Bloch, J H and Manax W G. Nature of irreversible shock: Experimental and clinical observations, Ann. Surg 160:682 1964
13 Hardaway R. M., James, P M Anderson, R. W., Bredenberg, C. E. and West, R. L: Intensive study and treatment of shock in man, J.A.M.A. 199:779 1967
14 MacLean, L. D Duff J H. Scott, H. M., and Peretz, D I Treatment of shock in man based on hemodynamic diagnosis, Surg. Gynec. Obstet. 120:1 1965.
15. Krasnow N Rolett, E. L. Yurchak, P M Hood W B., Jr and Gorlin, R. Isoproterenol and cardiovascular performance, Amer J Med. 37:514 1964.
16. Kardos, G G. Isoproterenol in the treatment of shock due to bacteremia with gram negative pathogens, New Eng J Med. 274:868, 1966.
17 Weil M H and Shubin, H. Isoproterenol for the treatment of circulatory shock, Ann. Intern. Med. 70:638, 1969
18. McCannell, K. L. McNay J L., Meyer M B., and Goldberg, L. I Dopamine in the treatment of hypotension and shock, New Eng J Med. 275:1389 1966.
19 Wilson R. F Jablonski, D V and Thal, A P : Usage of dibenzyline in clinical shock, Surgery 56:172 1964.
20. Lillehei, R C. Longerbeam J K., Bloch, J H and Manax W G Modern treatment of shock based on physiologic principles, Clin. Pharmacol. Ther 5:63 1964
21 Melby J C. Corticosteroids in shock in man and animals, New Physician 13:426, 1964.
22. Sambhi, M P Weil M H and Udhoji, V N Acute pharmacodynamic effects of glucocorticoids on cardiac output and related hemodynamic changes in normal patients and patients in shock, Circulation 31:523 1965.
23 Spink, W W Bacteremic shock, Hosp. Med. 2:24 1966.
24 Cavanagh, D Clark, P J and McLeod, A. G W Septic shock of endotoxin type, Amer J Obst. Gynec. 102:13 1968.
25. Wilson R. F., and Fisher R. R.: The hemodynamic effects of massive steroids in clinical shock, Surg Gynec. Obstet. 127:769 1968.
26. Blair E. Wise, A., and Mackay A. G. Gram negative bacteremic shock: Mechanisms and management, J.A.M.A. 207:333 1969
27 Spink, W W : Endotoxin shock, Ann. Intern. Med. 57:538 1962.

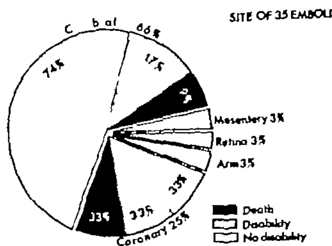


Fig. 1 Location of 35 emboli, with percentage of fatal outcome and permanent disability

Table I. Prosthetic valve replacement in 170 patients: site and sex distribution

Position		No. of patients	Sex M	Sex F
Isolated aortic		60	42	18
Isolated mitral		78	30	48
Isolated tricuspid		3	2	1
Mitral + aortic	Multiple	22		
Mitral + tricuspid	Multiple	4		
Triple	Multiple	3		
Multiple (total)		29	13	16

Table II. Occurrence of embolism according to the position of prosthesis

Position	No. of patients	Patients with one or more emboli	%
Aortic	60	9	15
Mitral	78	13	17
Multiple	29	5	17

other because of difficulties in controlling the prothrombin time or because of drug intolerance; thus, 1 0 patients had 212 courses of treatment, 77 with acenocoumarol and 135 with sodium warfarin.

The prothrombin time was determined by the Quick one-stage test at intervals of one to four weeks according to the stability of values. The aim was to maintain the level at or below 30 per cent (more than one and one-half times control time). Few patients could be maintained consistently with values below 30 per cent over the months and years of follow-up. Thus, for each patient the number of values above 30 per cent was related to the total number of values recorded and expressed in per cent; this ratio was used to judge the consistency of anticoagulant treatment.

Embolic episodes were diagnosed on clinical grounds: sudden cerebrovascular accidents, transient ischemic attacks, myocardial infarction without previous evidence of coronary artery disease, and sudden peripheral ischemia. When available, autopsy reports were also used (4 of the 5 fatal emboli). Embolic episodes occurring during operation and within 4 weeks postoperatively are not included in this series.

Results

Embolic episodes occurred in 27 patients (16 per cent). Five patients suffered more than one episode; the total number of embolic accidents was 35, 5 of which were fatal (14 per cent). Sites and complications are shown in Fig. 1. Cerebral emboli were predominant (23): 2 fatal, 4 with residual disability, and most with complete recovery. Of 9 coronary emboli, 3 proved fatal and 3 were followed by either heart failure or intractable arrhythmias. One brachial artery, one retinal, and one mesenteric occlusion were recorded.

As shown in Table II, the incidence of

Thromboembolic complications of heart valve prostheses

Beat Friedli, M.D.
Nicolas Aerichide, M.D.
Pierre Grondin, M.D.
Lucien Campeau, M.D.
Montreal, Quebec, Canada

Systemic emboli have been a major threat following replacement of cardiac valves.[1-13] Attempts to reduce this risk include anticoagulant drugs,[1-4] pharmacologic agents reducing platelet adhesiveness,[13,15] and partial or total covering of metal parts by Dacron or Teflon.[12,14,16] Anticoagulation has been widely used, although the effectiveness of a consistently well controlled treatment in reducing the risk of emboli has not always been clearly established.[1] Lately, the need for anticoagulant drugs has been questioned again as it appeared that completely cloth-covered prostheses bear a low risk of thromboembolic complications.[16,18] The present study was designed to appraise the value of anticoagulant drugs in reducing embolic complications of prosthetic valves.

Methods and material

The records of all patients operated on for cardiac valve replacement at the Montreal Heart Institute and followed in our anticoagulant clinic at one to four week intervals from the time of surgery until September, 1969, or until death were reviewed. This group contains approximately one fourth of all patients operated on for valve replacement from 1964 to June, 1969. The other patients did not attend the anticoagulant clinic because they did not live in the vicinity of the Heart Institute. Follow-up time ranged from 3 months to $5\frac{1}{2}$ years (mean 26 months).

The patients' age at operation ranged from 11 to 66 years, with a mean age of 44 years. There were 87 men and 83 women. Sixty patients had aortic valve replacement, 78 mitral, 3 tricuspid, and 29 multiple valve replacement (Table I). The total number of prostheses was 202: 175 Starr-Edwards, 14 Beall, 6 Hufnagel, 4 Magovern, one Smeloff-Cutter, one Gott and Daggett, and one Surgitool. Fifty-two patients received completely cloth-covered prostheses. Male patients were predominant in the aortic group, whereas women were found more numerous in the mitral group (Table I).

All received anticoagulant drugs starting within the first postoperative week. Acenocoumarol (Sintrom) or sodium warfarin (Warfilone, Coumadin) were used. Some patients were switched from one drug to the

From the Montreal Heart Institute, 5000 Belanger St., Montreal, Canada.
Received for publication July 10, 1970.
Reprint requests to: Dr. Nicolas Aerichide, Department of Cardiology, Institut de Cardiologie de Montreal, 5000 Est, Rue Belanger 36, Quebec, Canada.

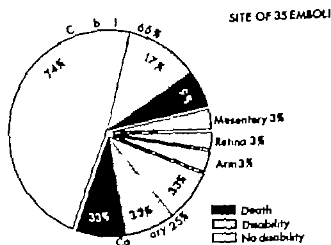


Fig. 1 Location of 35 emboli, with percentage of fatal outcome and permanent disability

Table I. Prosthetic valve replacement in 170 patients: site and sex distribution

Position		No. of patients		Sex M	Sex F
Isolated aortic		60		42	18
Isolated mitral		78		30	48
Isolated tricuspid		3		2	1
Mitral + aortic	Multiple	22	29	13	16
Mitral + tricuspid		4			
Triple		3			

Table II. Occurrence of embolism according to the position of prosthesis

Position	No. of patients	Patients with one or more emboli	%
Aortic	60	9	15
Mitral	78	13	17
Multiple	29	5	17

other because of difficulties in controlling the prothrombin time or because of drug intolerance; thus, 170 patients had 212 courses of treatment: 77 with acenocoumarol and 135 with sodium warfarin.

The prothrombin time was determined by the Quick one-stage test at intervals of one to four weeks according to the stability of values. The aim was to maintain the level at or below 30 per cent (more than one and one half times control time). Few patients could be maintained consistently with values below 30 per cent over the months and years of follow up. Thus, for each patient the number of values above 30 per cent was related to the total number of values recorded and expressed in per cent; this ratio was used to judge the consistency of anticoagulant treatment.

Embolic episodes were diagnosed on clinical grounds: sudden cerebrovascular accidents, transient ischemic attacks, myocardial infarction without previous evidence of coronary artery disease and sudden peripheral ischemia. When available, autopsy reports were also used (4 of the 5 fatal emboli). Embolic episodes occurring during operation and within 4 weeks postoperatively are not included in this series.

Results

Embolic episodes occurred in 27 patients (16 per cent). Five patients suffered more than one episode; the total number of embolic accidents was 35, 5 of which were fatal (14 per cent). Sites and complications are shown in Fig. 1. Cerebral emboli were predominant (23): 2 fatal, 4 with residual disability, and most with complete recovery. Of 9 coronary emboli, 3 proved fatal and 3 were followed by either heart failure or intractable arrhythmias. One brachial artery, one retinal, and one mesenteric occlusion were recorded.

As shown in Table II, the incidence of

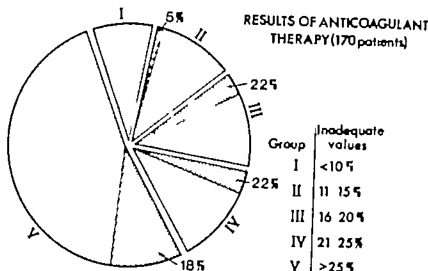


Fig 2 Results of anticoagulant therapy Prothrombin time longer than one and one-half time control time (30 per cent or less) are considered adequate shorter time inadequate Patients are divided in groups according to the rate of inadequate levels occurring during follow-up Shaded areas indicate incidence of embolism in each group Group I includes 14 patients, no emboli Group II 19 patients, 1 with embolism Group III 25 patients, 5 with embolism Group IV 23 patients, 5 with embolism and Group V 91 patients, 16 with embolism.

thromboembolic episodes in mitral aortic and multiple prostheses is similar

Anticoagulant therapy Fig 2 shows five groups of patients divided according to the consistency of anticoagulant therapy as judged by the ratio of values above 30 per cent to the total number of values recorded expressed in per cent The incidence of emboli appears to be very low in patients of Group I and II ($\leqslant$ 15 per cent inadequate values) whereas patients with a score of 15 to 20 per cent and 20 to 25 per cent have a higher incidence as well as those with more than 25 per cent values outside the therapeutic range As there appears to be a threshold at 15 per cent we compared all patients with a score of 15 per cent or less (A) to the remaining patients (B) The incidence of emboli is 3 per cent in the former group as compared to 19 per cent for the latter (Fig 3) The difference is statistically highly significant ($p < 0\ 001$) The groups appear to be well matched for follow up time (28 6 $\pm$ 16 9 and 25 5 $\pm$ 16 6 months) and age (41 5 and 44 5 years)

Prothrombin time on the day the embolic episode occurred is known in 25 of 35 episodes. Fourteen times (56 per cent) the value was above 30 per cent (less than one and one-half time control time)

As demonstrated in Fig 4 aortic, mitral and multiple prostheses likewise benefited

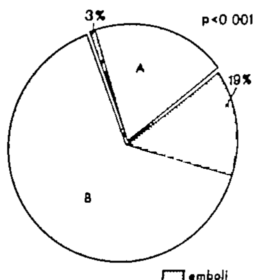


Fig 3 Incidence in a group (A) with good anticoagulant control (15 per cent or less inadequate values) as compared to a group (B) with less satisfactory control (more than 15 per cent inadequate values) (A) comprises 33 patients, 1 with embolism; (B) 137 patients, 16 with embolism.

from a good control of prothrombin time.

Atrial fibrillation Seventy nine of 170 patients had atrial fibrillation (46 per cent) These were mostly patients with mitral or multiple valve replacement (71 per cent of patients with mitral and 62 per cent of patients with multiple replacement, versus 7 per cent of patients with aortic replacement) Thirteen (16 per cent) patients with atrial fibrillation suffered one or more

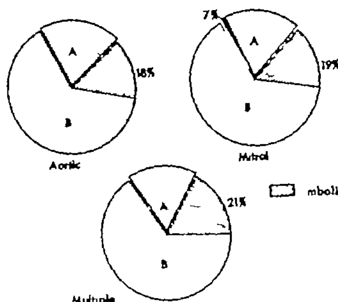


Fig. 4 Same as Fig. 3, considering separately patients with aortic, mitral, and multiple valve prostheses. Aortic: Grade *A* 12 patients, no emboli. Grade *B* 48 patients, 9 with emboli. Mitral *A* 15 patients, 1 with embolism. *B* 63 patients, 12 with emboli. Multiple: *A*, 5 patients, 0 emboli. *B*, 24 patients, 5 with emboli.

emboli, versus 14 (15 per cent) of 91 patients in sinus rhythm. Thus, atrial fibrillation is not an additional risk factor

Emboli related to the year of operation. Incidence of emboli was higher in patients operated on during the early years of valve replacement surgery. In this series there was an incidence of 64 per cent in patients operated in 1964 versus 6 per cent in 1968 (Fig 5)

Timing of thromboembolic episodes. Within the first and second year of follow-up the incidence of emboli was 8 per cent and 6 per cent respectively whereas a 5 per cent incidence is recorded during the third and fourth year. There have been no emboli in the fifth and sixth year of follow-up (Fig 6).

Type of anticoagulant drug. Well-controlled courses of treatment, in our hands, have been more often achieved with sodium warfarin (33 in 135) than with Acenocoumarin (9 in 77 courses). Less embolic episodes occurred during sodium warfarin (7 in 135 courses) than during Acenocoumarin treatment (27 in 77). However it has to be pointed out that sodium warfarin has been used only since 1967 whereas in the early years, 1964 to 1967 Acenocoumarin was exclusively prescribed.

Cloth-covered prosthesis. These include

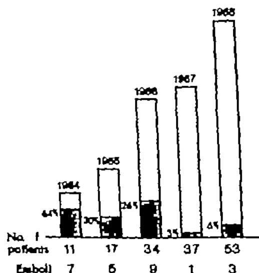


Fig. 5 Rate of emboli according to the year of operation.

Starr 6300 6310 2300 2310, Beall disc prostheses, and Surgitool prostheses. These models came into use in November 1967. Completely cloth-covered prostheses were implanted in 52 patients. Only two (4 per cent) had thromboembolic episodes so far (follow-up time 3 to 21 months) as compared to an incidence of 11 per cent (3 of 28) in the group of patients with partially

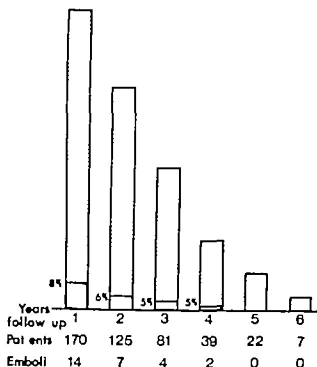


Fig 6 Timing of emboli There seems to be a decreasing incidence during the first 4 years of follow up No new emboli occurred during the fifth and sixth year

cloth-covered prostheses (bare struts) operated on during the same period (November 1967 to June 1969) (Fig 7) Since the consistency of anticoagulant therapy was the same in these two groups it appears that the statistically significant difference ($p < 0.001$) is due exclusively to cloth covering

Hemorrhagic complications of anticoagulant treatment Hemorrhagic phenomena were reported by half of the patients (Fig 8) Thirty nine per cent had benign episodes like bruises epistaxis and minor hematomas. Ten per cent had serious hemorrhage necessitating hospital care and transfusions In most instances Two patients died (1 2 per cent) one of severe retroperitoneal hemorrhage and the other one of diffuse gastrointestinal tract bleeding

Discussion

The use of anticoagulant drugs to prevent thromboembolism from prosthetic heart valves has been widely accepted [1-4] however while some investigators find a much higher incidence of emboli in patients with no anticoagulant treatment [1,3] others fail to demonstrate a significant difference [2] On the other hand some authors report less embolic complications in patients with adequate versus those with inadequate anticoagulant therapy [2,4] whereas others do not.[1] This may depend on the criteria used. Precise assessment of adequate therapy needs close follow up which was achieved in all 170 patients reported in this series. It appears also that the consistency of the anticoagulant treatment is of the utmost importance and in our experience only patients with very few ($\leq$ 15 per cent) prothrombin time values outside the therapeutic range have significantly less embolic complications. In patients of our series with slightly higher scores (15 to 25 per cent) who could have been classified as good control using the criteria of Akbarian [1] the incidence of embolic complications is comparable to that of the poorly controlled patients. It appears that embolism from prosthetic material can be almost completely avoided when patients have consistently therapeutic levels of prothrombin time It has been stated that the incidence of thromboemboli is higher in mitral than aortic prosthesis,[3,4,6] and higher in multiple than in isolated valve replacement.[4] Along with Duvoisin[2] we did not find a significant difference The three groups are comparable since adequacy of anticoagulation has been about similar in all three.

Atrial fibrillation often has been found an additional risk factor causing increased incidence of embolism [3,4,6] There has been no significant difference in the present series between patients with atrial fibrillation and those in sinus rhythm This is in agreement with data from some other investigators.[1,4,6]

Since the early years of cardiac valve replacement incidence of thromboembolism has been steadily decreasing This is mostly due to better valve design[12] but also to improvement of surgical technique and extracorporeal circulation especially the use of hemodilution [8] This decreasing incidence of embolism is striking in the present series The longer follow up time of patients operated on in 1964 to 1966 accounts only partly for the high incidence since there is a tendency toward decreasing risk as years pass by The actuarial curves of Duvoisin[2] and Akbarian[1] show a levelling off after 2 years. The statistics of Starr and his group[12,13] show a decreased incidence in the

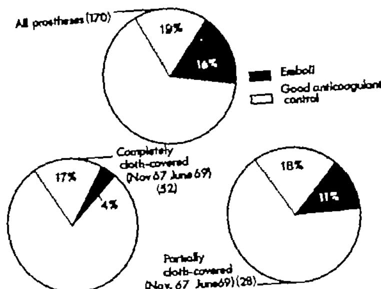


Fig. 7 Incidence of thromboembolism in patients having completely cloth-covered prostheses (52 patients, 2 with emboli) as compared to overall incidence and to a control group of patients having received partially covered prostheses during the same 19 months (28 patients, 3 with emboli) $p < 0.001$ Dark areas are emboli, shaded areas, percentage of consistently well anticoagulated patients.

third and fourth year follow-up and no emboli in the fifth and sixth year This is quite similar to our findings There was no new embolic episode in the fifth and sixth year follow-up and a tendency toward decreasing risk in the third and fourth year The fact that sodium warfarin which in our hands gave somewhat better control of prothrombin time than Acenocoumarin, was used in the last three years only may account for some decrease in embolism. More important appears to be the use of cloth-covered prosthesis. Partial covering of metal parts already proved to be of benefit[18] and the first reports on totally cloth-covered prosthesis are even better With the cloth-covered Starr Edwards prosthesis the overall incidence of late embolism has been 5 per cent the 6300 model (mitral) has yielded better results (3 per cent) than the 2300 (aortic) (6 per cent) The Beall prosthesis is said to have an incidence of 2 per cent thromboembolic complications. No emboli are reported by Linhart in 21 Beall prostheses. In the present series the overall incidence of embolism in completely covered valves has been 4 per cent during a follow-up time of 3 to 21 months, whereas an incidence of 14 per cent based upon our yearly rate of emboli would have been expected. These data are best compared to

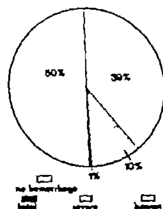


Fig. 8 Hemorrhagic complications in 170 patients receiving anticoagulants.

an 11 per cent incidence of thromboembolism occurring in partially covered valves implanted during the same period. These two groups are small but well-matched as operation was carried out during the same months and the ratio of good anticoagulation is the same in both, and the difference is highly significant ($p < 0.001$)

It appears that the possible advantage of further anticoagulating patients carrying cloth-covered devices has to be weighed against the risk of hemorrhagic complications. This risk has been, in the present

series, 10 per cent for severe hemorrhage and 1 per cent for fatal bleeding We do not know how effective anticoagulant treatment has been in avoiding embolism in our series since all were anticoagulated but double blind studies as the one undertaken in Portland[18] are certainly justified and should provide an answer soon Complete healing of the cage including the struts does occur and no emboli were recorded by Hodam[18] after ten months postoperatively The same can be said in our series where the two episodes occurred in the sixth and seventh month This could be an argument in favor of temporary anticoagulation covering the period from operation to complete healing of the cloth-covered prosthesis.

Summary

One hundred seventy patients with prosthetic heart valves receiving anticoagulant therapy have been followed at one to four week intervals for three to sixty-eight months (mean 26 months) The overall incidence of late emboli was 16 per cent. The risk was approximately the same for patients carrying aortic mitral and multiple prostheses. Consistently good control of prothrombin time (0 to 15 per cent of recorded values outside the therapeutic range) is effective in reducing the incidence of thromboembolism which was 3 per cent in these patients. Atrial fibrillation has not been an additional risk factor The incidence of embolic episodes has a tendency to decrease in the third and fourth year postoperatively and no emboli were recorded during the fifth and sixth year follow up Completely cloth-covered prostheses appear to bear a low risk of thromboembolic complications (4 per cent in the present series)

REFERENCES

1 Akbarian, M Austen, W G Yurchak, P M and Scannel J G Thromboembolic complications of prosthetic cardiac valves, Circulation 37:826, 1968.
2. Duvoisin, G. E., Brandenburg, R. O and Mc Goon, D D: Factors affecting thromboembolism associated with prosthetic heart valves, Circulation 35-36:(Suppl. I) 70, 1967
3 Yeh T J Anabtawi, I. N., Cornett, V E. and Ellison, R. G.: Influence of rhythm and anticoagulation upon the incidence of embolization associated with Starr Edwards prostheses, Circulation 35-36:(Suppl. I) 77 1967
4. Penther P H Bensaid, J., Maurice, P and Lenegre, J Les complications thromboemboliques après remplacement valvulaire par la prothèse de Starr Edwards, Arch. Mal. Coeur 61:1278, 1968.
5 Matloff J M Collins, J J Sullivan, J M., Gorlin, R., and Harken, D E. Control of thromboembolism from prosthetic heart valves, Ann. Thorac. Surg. 8:133 1969
6. Herr R Starr A., McCord C. W., and Wood, J A. Special problems following valve replacement, Ann. Thorac. Surg 1:403, 1965.
7 Duvoisin, G E. Wallace, R. B Ellis, F H., Anderson M W and McGoon, D C. Late results of cardiac valve replacement, Circulation 37-38:(Suppl. II) 75 1968.
8. Fishman, N H. Hutchinson, J C., Masengale, M M., and Roe, B. B: Follow-up evaluation of 100 consecutive mitral prosthesis implants, Arch Surg 97:691 1968.
9 Najafi H Dye, W S. Javid, H Hunter J A. Ostermiller W E., and Julian O C.: Mitral valve replacement, review of 7 years experience, Amer J Cardiol. 24:386, 1969
10. Fleming J Hamer J Hayward, G. Tubbs, O S. and Hill I Long term results of aortic valve replacements with the Starr Edwards valve, Brit. Med. J 1:139 1969
11 Mulder D G., and Rosenthal B. P Late results with Starr valve replacement of the aortic valve, J Cardiovasc. Surg 9:440, 1968.
12. Herr R. H Starr A. Pierie, W R., Wood J A. and Bigelow J C.: Aortic valve replacement, a review of 6 years experience, Ann. Thorac. Surg 6:199 1968.
13 Bigelow J C. Herr R. H Wood J A. and Starr A. Multiple valve replacement: Review of 5 years experience, Circulation 38:656, 1968.
14 Penther P H., Bensaid J., Maurice, P and Lenegre, J: Résultats éloignés et risques du double remplacement valvulaire mitral et aortique par prothèses à bille, Arch. Mal. Coeur 61:519 1968.
15. Sullivan J M Harken, D E., and Gorlin, R. Pharmacologic control of thromboembolic complications of cardiac valve replacement, New Engl J Med. 279:576, 1968.
16. Beall, A. C. Bloodwell R. D Liotta, D Cooley D A. and DeBakey M E: Clinical experience with a Dacron velours covered Teflon disc mitral valve prosthesis, Ann. Thorac. Surg 5:402, 1968.
17 Linhart, J W Barold S. S., Hildner F J Samet, P H Piccinini, J C. Marsten, J L., and Greenberg, J J Clinical and hemodynamic findings following replacement of the mitral valve with a Beall valve prosthesis, Circulation 49:(Suppl. I) 127 1969
18. Hodam, R. Starr A., Herr R., and Pierie, W R. Early clinical experience with cloth-covered valvular prostheses, Ann. Surg. 170:471 1969
19 Sullivan J M., Harken, D E., and Gorlin, R.: Effect of dipyridamole on the incidence of arterial emboli after cardiac valve replacement, Circulation 39:(Suppl. I) 149 1969

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Julian Frieden

Drug interactions in the therapy of cardiovascular disorders

Ilene H. Raisfeld, M.D.
New York, N. Y.

The increasing number of effective drugs has made possible significant advances in the therapy and understanding of cardiovascular disease. At the same time, it has become dramatically apparent that the practice of administering a number of therapeutic agents concomitantly has created a whole new era of mischief often with disastrous results to the patient. Both enhanced appreciation of the mechanisms of drug action and the alarming increase in the number of reported adverse drug reactions have, in part, led to the development of a new kind of medical ombudsman, the linical pharmacologist. By understand g the various ways in which drugs may teract with each other and the lim t g treatment to those drugs which are ab lutely necessary t is hoped that future erapeutic misadventures can be avoided.

Appreciation of drug interactions is en nced by understanding the fundamental rinciples of drug handling. From the time drug enters the body until it is eliminated : has interacted with a multiplicity of nding proteins, enzymes, organs, and eceptor sites. These general pathways will e reviewed in this presentation. Subsequent publications in this series will elaborate further details of specific classes of drugs. *The accompanying table* (Table I) summarizes the different ways in which drugs may interact.

Improper preparation of medication

Improper preparation of the medication, by introduction into the wrong solution or addition to other medications with which it is incompatible may produce a source of trouble even *before* the drug has reached the patient. For example, levarterenol should be administered with dextrose-containing solutions to prevent its oxidation. Regular insulin binds to glass, while some drugs such as digoxin, digitoxin barbiturates, and tetracyclines will be bound by protein hydrolysates. Metaraminol in solution is incompatible with diphenylhydantoin methicillin and potassium penicillin.

Mode of administration

The mode by which a drug is administered may also influence both desired and undesired effects. For many agents, higher blood levels tend to be realized sooner by the intravenous rather than the oral or intramuscular route. The tetracyclines, which are potent chelators, are capable of causing hypocalcemic tetany if infused too rapidly. In general drugs which have

From the Stalla and Charles Gettman Laboratories for Human Pharmacology and Pharmacogenetics and the Department of Pharmacology, New York University School of Medicine, New York, N. Y.
Supported by Grant GM 7184 from the National Institute of General Medical Sciences.
Received for publication Dec. 28, 1970.

Assistant Professor, Department of Medicine, New York University School of Medicine, Assistant Attending Physician, University Hospital, and Assistant Visiting Physician, Bellevue Hospital.

Table I. Drug interaction mechanisms

- I In vitro
  - A Inactivation
  - B Incompatibility
- II Mode of administration
  - A Route
  - B Speed
  - C. Metabolism
  - D Gastrointestinal
    - 1 Solubility
    - 2 Interaction with other agents
    - 3 Alteration in flora
    - 4 Interaction with body constituents
- III Plasma albumin
  - A. Competitive
  - B Noncompetitive
  - C. Metabolite competition
- IV Receptor site
- V Nonspecific binding
- VI Hepatic transport proteins
- VII Biotransformation
  - A. Phase one—microsomal metabolism
    - 1 Induction-accelerated metabolism
    - 2 Inhibition
      - a Competitive
      - b Noncompetitive
  - B Phase two—conjugations (microsomal and nonmicrosomal)
    - 1 Induction
    - 2 Inhibition
      - a. Competitive
      - b. Noncompetitive
- VIII Hepatic excretory transport proteins
- IX Biliary excretion
  - A. Competition
  - B Bile salt metabolism
- X Pharmacologic effect
  - A. Interaction expected if pharmacologic action understood
- XI Renal excretion
  - A. Filtration
    - 1 Protein binding
  - B Reabsorption
    - 1 pH
    - 2 Liposolubility
  - C. Tubular secretion
    - 1 Competition for specific pathways
- XII In vitro
  - A. Alteration of laboratory tests
- XIII Genetic predisposition
- XIV Modification of drug handling by disease
- XV Diseases due to drugs

strongly acidic groups and basic groups will interact and neutralize each other This has been employed beneficially to counteract excess anticoagulation with acidic heparin by the administration of basic protamine sulfate.

One aspect just recently being appreciated is the influence of the route of administration on the metabolism of the drug For example isoproterenol administered by inhalation or intravenously is converted to 3-0 methyl isoproterenol a metabolite which has weak beta receptor *blocking* activity This does not occur after oral administration In contrast after oral administration of propranolol an active metabolite is found in the blood but this metabolite is not present if the drug is infused intravenously

Since the gastrointestinal tract behaves as a lipid membrane agents which are administered orally must pass through this membrane For most drugs, the nonionized form is also the most liposoluble, and in the nonionized form the drug is then distributed from an area of high concentration in the gut to the blood where it is in lower concentration Alterations in the intraluminal pH of the gastrointestinal tract can alter the amount of nonionized drug and thus affect the amount absorbed An elevated gastric pH can decrease the absorption of acidic drugs such as the oral anticoagulants, nalidixic acid and phenylbutazone but may increase the absorption of an acid labile drug such as penicillin G The gastric pH may be altered by antacids, other drugs present or as a result of the patient's disease In rats Hurwitz[1] has recently shown that antacid therapy can lower the rate of pentobarbital absorption nullifying the hypnotic effect even though the entire dose is eventually absorbed Aluminum hydroxide appears to decrease the rate of absorption by slowing gastric emptying time while magnesium hydroxide exerts its effect by raising the gastric pH

Cathartics may decrease drug absorption by increasing intestinal motility or may cause potassium depletion thereby potentiating the effects of certain drugs, such as digitalis. Antibiotics, by changing the intestinal flora may alter the response to other drugs as in the potentiation of oral anticoagulants by the elimination of the vitamin K synthesizing intestinal bacteria.

A drug may interact with a needed body constituent in the gastrointestinal tract, resulting in an adverse effect such as megaloblastic anemia Dietary folic acid is in

gested in a polyglutamic form and requires conversion into the monoglutamic form by the enzyme *folic acid conjugase* in order to be absorbed. Several drugs, i.e., triamterene, oral contraceptives, and diphenylhydantoin inhibit folic acid conjugase in the intestine or bone marrow of a small number of patients, who may have a genetically different enzyme. In these patients, megaloblastic anemia results.

Binding to plasma albumin

As a drug is absorbed, it usually binds to the plasma albumin to some degree and is then distributed throughout the body where binding to active receptor sites, inactive storage sites, sites of metabolism and excretion occurs. For most drugs, there is one major binding site to plasma albumin, and these sites are limited in number. One drug may interfere competitively with the binding of another drug to plasma albumin by competing for the same limited number of binding sites, or noncompetitively by binding at a different site on the albumin molecule, in a way which produces a conformational change in the molecule, preventing the binding of a second drug.

In the blood it is the unbound fraction of the drug which is pharmacologically active. Simultaneous administration of two drugs which are bound to plasma proteins may result in one drug displacing the other with increased pharmacologic activity of the second agent, increased action of both agents, or there may be no change in activity depending on the relative affinities of both agents for plasma albumin and the respective affinities for the other tissue binding sites. Displacement of a small fraction of a drug which is highly bound may result in a dramatic increase in pharmacologic activity. Warfarin is normally 97 per cent bound with only three per cent of drug free and active. If it is displaced by another drug from its binding site by only three per cent, the concentration of active warfarin doubles. Similar displacement of a drug which is 70 per cent bound would result in a much smaller increase in available free drug. In pharmacologic doses, any acidic drug significantly bound to albumin should be expected to displace other acidic drugs such as the coumarin anticoagulants, sulfonylureas, sulfonamides, phenylbutazone, clofibrate, and indomethacin. Diazoxide, ethacrynic acid, nalidixic acid, and mefenamic acid can increase the levels of warfarin by decreasing its protein binding. Acidic metabolites of a drug can also do this. Chloral hydrate is converted into an acidic metabolite, trichloroacetic acid, which can then displace warfarin and potentiate the anticoagulant effect. Methotrexate, a drug highly bound to plasma proteins, may be displaced from its binding sites by salicylates or sulfaphenazole, with a resultant increase in pancytopenia observed. Salicylates also compete with methotrexate for renal excretion, thus competing with methotrexate at two sites. In man important differences have been observed in the extent of protein binding of various drugs, such as digitoxin.

Binding to receptors and tissue proteins

In tissues, interaction of drugs with macromolecules or receptors results in a pharmacologic effect. Drugs also may bind without pharmacologic effect to nonreactive sites. Pharmacologically active, specific binding receptors are considered to have high affinity but low capacity, while nonspecific binding sites tend to have low affinity but high capacity. Certain barbiturates, phenothiazines, and cinchona alkaloids (i.e., emetine, quinine, and quinidine) are highly bound to nonreactive tissue proteins. The potent arteriolar dilator diazoxide, must be injected rapidly intravenously to achieve maximum hypotensive action in the treatment of severe hypertension. This drug is highly bound to protein and the kinetics have suggested that the receptor sites must be filled rapidly for achievement of the desired therapeutic response.

The pharmacologic response of a drug may also be influenced by factors which alter the affinity of the drug for its receptor site. Vitamin K and warfarin may compete for a common receptor site in the liver and thereby influence the rate of synthesis of clotting factors. D-thyroxine may increase the affinity of warfarin for its receptor site, and thus potentiate the action of the anticoagulant. Atropine and acetylcho-

Table I Drug interaction mechanisms

I In vitro
  A. Inactivation
  B Incompatibility
II Mode of administration
  A. Route
  B Speed
  C Metabolism
  D Gastrointestinal
    1 Solubility
    2 Interaction with other agents
    3 Alteration in flora
    4 Interaction with body constituents
III Plasma albumin
  A. Competitive
  B Noncompetitive
  C. Metabolite competition
IV Receptor site
V Nonspecific binding
VI Hepatic transport proteins
VII Biotransformation
  A Phase one—microsomal metabolism
    1 Induction-accelerated metabolism
    2 Inhibition
      a. Competitive
      b Noncompetitive
  B Phase two—conjugations (microsomal and nonmicrosomal)
    1 Induction
    2 Inhibition
      a. Competitive
      b Noncompetitive
VIII Hepatic excretory transport proteins
IX. Biliary excretion
  A Competition
  B Bile salt metabolism
X Pharmacologic effect
  A. Interaction expected if pharmacologic action understood
XI Renal excretion
  A. Filtration
    1 Protein binding
  B Reabsorption
    1 pH
    2 Liposolubility
  C. Tubular secretion
    1 Competition for specific pathways
XII In vitro
  A. Alteration of laboratory tests
XIII Genetic predisposition
XIV Modification of drug handling by disease
XV Diseases due to drugs

strongly acidic groups and basic groups will interact and neutralize each other This has been employed beneficially to counteract excess anticoagulation with acidic heparin by the administration of basic protamine sulfate.

One aspect just recently being appreciated is the influence of the route of administration on the metabolism of the drug For example isoproterenol administered by inhalation or intravenously is converted to 3-0-methyl isoproterenol a metabolite which has weak beta receptor *blocking* activity This does not occur after oral administration In contrast after oral administration of propranolol an active metabolite is found in the blood but this metabolite is not present if the drug is infused intravenously

Since the gastrointestinal tract behaves as a lipid membrane agents which are administered orally must pass through this membrane. For most drugs, the nonionized form is also the most liposoluble and in the nonionized form the drug is then distributed from an area of high concentration in the gut to the blood where it is in lower concentration Alterations in the intraluminal pH of the gastrointestinal tract can alter the amount of nonionized drug and thus affect the amount absorbed An elevated gastric pH can decrease the absorption of acidic drugs such as the oral anticoagulants, nalidixic acid and phenylbutazone, but may increase the absorption of an acid labile drug such as penicillin G The gastric pH may be altered by antacids, other drugs present or as a result of the patient's disease In rats, Hurwitz[1] has recently shown that antacid therapy can lower the rate of pentobarbital absorption nullifying the hypnotic effect even though the entire dose is eventually absorbed Aluminum hydroxide appears to decrease the rate of absorption by slowing gastric emptying time while magnesium hydroxide exerts its effect by raising the gastric pH

Cathartics may decrease drug absorption by increasing intestinal motility or may cause potassium depletion thereby potentiating the effects of certain drugs, such as digitalis. Antibiotics, by changing the intestinal flora may alter the response to other drugs as in the potentiation of oral anticoagulants by the elimination of the vitamin K synthesizing intestinal bacteria

A drug may interact with a needed body constituent in the gastrointestinal tract resulting in an adverse effect such as megaloblastic anemia Dietary folic acid is in

to increase their own metabolism on continued administration or increase the metabolism of other compounds handled by the same system. This explains some instances of tolerance, where the drug enhances its own metabolism and the dose of a drug must be increased on continued administration to maintain a constant pharmacologic effect. The patient who requires more and more barbiturates in order to fall asleep is such an example.

The dangers in the concomitant administration of anticoagulants and sedatives in the patient with an acute myocardial infarction have been widely publicized with good reason. Many barbiturates and sedatives, by inducing microsomal enzymes, accelerate the metabolism of oral anticoagulants. While both drugs are administered together the dose of anticoagulant is that which maintains the desired effect on the prothrombin time. As the patient improves, sedation is often discontinued while anticoagulation is maintained. As the sedatives are no longer accelerating the inactivation of the anticoagulants, the anticoagulant blood levels and pharmacologic effect may increase markedly resulting in serious bleeding unless the dose of anticoagulant is lowered.

Since classes of drugs share the same pathways of inactivation two agents handled by the same system may inhibit each others metabolism when administered *acutely*. On *chronic* administration, the capacity of the drug metabolizing system may be increased by induction, with resultant enhanced inactivation of one or both drugs.

As drugs may increase the inactivation of other agents, one drug may also inhibit the metabolism of a second drug. Chloramphenicol has been shown to inhibit the biotransformation of tolbutamide, diphenylhydantoin, and dicumarol in man. Isoniazid inhibits the nonmicrosomal metabolism of diphenylhydantoin but toxic reactions to the increased diphenylhydantoin levels tend to be seen in genetically determined slow inactivators of the drug. Two drugs, iproniazid and triparanol (MER 29) now known to be inhibitors of the drug metabolizing system of liver microsomes, were so toxic that their sale was discontinued.

Studies of the metabolism of antipyrine, phenylbutazone, tolbutamide, desmethyl imipramine nortriptyline, and vitamin K in twins and in related and nonrelated individuals suggest that the rate of metabolism can vary markedly in individuals and is genetically determined. Which hepatic factors are most important in limiting the rate of drug metabolism in man have not yet been completely elucidated. The rates of metabolism of drugs are influenced not only by genetic factors and other drugs as mentioned, but also by exposure to such diverse environmental factors as insecticides, cigarette smoking, the use of coffee, tea, alcohol, hormones, and diet. Probably all of man's virtues and vices will be found to affect this system in one way or another.

Conjugations—phase two. In contrast to the appreciable information available regarding microsomal biotransformation relatively little is known of the drug conjugation (phase II) mechanisms in man. It is known that several glucuronyl transferases exist in the liver. These enzymes transfer glucuronic acid to drugs and endogenous substrates such as bilirubin. Competition for a microsomal (but not P-450-requiring) pathway has been shown by the concomitant administration of salicylamide and sodium salicylate to healthy adults. These drugs, which are readily available to the public, share a low capacity glucuronidation pathway resulting in a competitive inhibition of their respective metabolites.

Hepatic export proteins?

Studies of children with congenital unconjugated hyperbilirubinemia have distinguished at least two populations with respect to the glucuronyl transferase involved in the conjugation of bilirubin. One group appears to completely lack glucuronyl transferase. In another group this enzyme may be absent but inducible by such drugs as phenobarbital. Transfer proteins, such as the Y protein are deficient in physiologic neonatal jaundice and the role of these proteins in congenital unconjugated hyperbilirubinemia is being defined. The type of information just described suggests that much more information is needed regarding genetic differences

line bind to the same receptor Atropine antagonizes the transmitter action of acetylcholine because it has a higher binding affinity and no intrinsic pharmacologic activity Cholinesterase inhibitors, such as neostigmine and edrophonium raise acetylcholine levels and reverse the action of atropine By blocking the alpha receptors phentolamine inhibits the action of norepinephrine while the action of isoproterenol is inhibited by the beta receptor blockade effected by propranolol Propranolol may potentiate insulin hypoglycemia by antagonizing the hyperglycemic effects of catecholamines.

Hepatic transport proteins

Most drugs reach the liver where they are taken up by the hepatocyte in order to be converted into metabolites which can then easily be eliminated from the body The role of transport proteins in the carriage of drugs into the liver is just being appreciated Two hepatic intracellular cytoplasmic proteins Y and Z have been described recently They function in the transfer of bilirubin bromsulphalein (B.S P) and other organic anions from plasma into the liver cell Y is the major binding protein and can be increased in vivo by the administration of drugs such as phenobarbital and may be regulated by pituitary and thyroid hormones. It is likely but yet unproved that these or similar proteins play an important role in the transport of drugs into the liver cell It is probable that classes of drugs as well as endogenous substrates compete for sites on these proteins and that the capacity of this system is genetically determined

Hepatic biotransformation

Teleologically R T Williams[4] has viewed drug metabolism as a two-phase process which ensures the elimination of the drug from the body In the first place drugs are transformed in the endoplasmic reticulum (microsomal fraction) into compounds which are more the same, or less active than the parent agent by reactions which can be viewed as biological oxidations. In the second phase the parent compound or phase one metabolites undergo conjugations with such substances as glucuronic acid resulting in metabolites less active than the parent drug Glucuronidation is carried out in the endoplasmic reticulum but the other conjugations, such as acetylation occur in the soluble fraction of the liver The metabolites which result are less liposoluble than the parent compound thus insuring their elimination by the kidney which in contrast to the liver acts as a barrier to lipids.

Microsomal oxidations—phase one The hepatic drug metabolizing system is nonspecific in the sense that it can metabolize compounds it has never seen before, permitting the body to process hundreds of drugs chemicals, carcinogens, and environmental agents. Moreover the presence of many of these agents has the ability to increase the capacity of this system by the process of enzyme induction Exactly how the drugs effect an increase of the enzymes which metabolize them is not yet completely understood but in part may be due to an effect on (ribonucleic acid) RNA polymerase

A wide variety of phase one biotransformations are mediated by a class of hemeprotein enzymes called P-450 because of their unusual spectral properties. Via a two electron transfer hemeprotein P-450 activates molecular oxygen resulting in an oxidized drug and water Although many important reactions in this system are literally biological oxidations, such as hydroxylation reactions some are reductions such as nitroreduction

In order to catalyze these reactions, cytochrome P-450 must be reduced In the liver this transfer of electrons is mediated by another enzyme P-450 reductase which may be the same or similar to cytochrome C reductase Studies in animals suggest that the rate of P-450 reduction rather than the amount of hemeprotein P-450 present, determines the rate of drug metabolism This capacity may be determined genetically

Many drugs and environmental agents have the capacity to induce or increase the components of the drug metabolizing system resulting in an increase in the amount of endoplasmic reticulum membranes, hemeprotein P-450 and P-450 reductase. By this mechanism many drugs are able

impairment alters the detoxification and excretion of drugs, only recently is it becoming clear that in many diseases the absorption distribution metabolism and even the receptor action may be altered and may significantly affect the response to the drug

Cardiovascular disease caused by drugs

As the use of drugs increase more and more diseases due to drugs are being recognized. Of particular interest are reactions to nitrofurantoin which simulate pulmonary edema, hypertensive crises in patients receiving monamine oxidase inhibitors, arrhythmias caused by L-dopa cardiac toxicity from aerosol propellants, myocardiopathy due to isoproterenol and bleeding caused by the surreptitious administration of anticoagulants.

Fortunately a number of effective therapeutic agents are now available which save countless patients and extend useful lives for many years. The frequency of multiple drug therapy particularly in cardiovascular disorders, requires understanding of how these agents work, so that they may be used wisely and well

REFERENCES

1 Azarnoff D L and Hurwitz, A. Drug interactions, Pharmacol. Physicians 4 1, 1970
2. Solomon, H. M Clinical disorders of drug interaction, Advances I tern. Med. 16:285 1970.
3. Mannering, G M. Drug interactions, Chronic non-psychiatric hazards of drugs of abuse, Washington, D C., 1971, Government Printing Office.
4. Conference on drug metabolism in man, Ann. N Y Acad. Sci. I press.
5. Prescott, L. F Pharmacokinetic drug interactions, Lancet 2 1239 1969
6. Williams, R. T Detoxication mechanisms, London, 1959 Chapman & Hall, Ltd.

in conjugations of drugs as well as the transport mechanism involved in the elimination of these metabolites from the liver cell

The genetics of N acetyltransferase the enzyme which acetylates such drugs as isoniazid hydralazine and sulfamethazine have been well investigated Kinetic studies indicate differences in the catalytic properties of enzymes isolated from rapid and slow inactivators of these drugs.

Predicting certain reactions

Some types of drug interactions can be predicted and avoided if the pharmacologic action of the drug is kept in mind For instance allopurinol inhibits the enzyme xanthine oxidase thus decreasing the production of uric acid Two other drugs azothioprine and 6-mercaptopurine are themselves inactivated by the enzyme xanthine oxidase Therefore it is not surprising that severe bone marrow depression may result from such a combination of drugs The use of monamine oxidase inhibitors results in the accumulation of biogenic amines. A marked pressor response may then occur if these agents are given with drugs which release norepinephrine from the adrenergic neuron Chlorpropamide and tolbutamide inhibit the enzyme alcohol dehydrogenase which metabolizes alcohol This explains ethanol intolerance observed with these agents.

Renal elimination

Filtration and reabsorption Although drugs may be eliminated via the lungs, in the bile and in the milk for most drugs the kidney is the major organ of elimination The unbound fraction of a drug will appear in the glomerular ultrafiltrate As in the gastrointestinal tract the liposolubility and the proportion of the drug which is ionized affects tubular reabsorption Since the renal tubule behaves as a lipid membrane nonionized drug will be reabsorbed while the *ionized drug is not* reabsorbed and will pass into the urine. Weak bases, such as the amphetamines, are rapidly excreted in an acid urine but slowly excreted if the urine is alkaline. Sulfadiazine (pK 6 5) is a weak acid Less than one per cent will be ionized at a urinary pH of 4 0 while the drug is 97 per cent ionized at pH 8 0 Thus the *intensity and duration* of the drug action can be markedly influenced by ammonium chloride vomiting, metabolic acidosis and other factors which affect the pH of the urine.

Tubular secretion The tubular secretory process handles organic cations and anions by separate mechanisms. Here all of the drug whether *reversibly bound to protein* or free is available for secretion by the tubules The tubular transport secretory capacity is limited and characteristic maximum secretion rates can be calculated The anion secretion system functions to eliminate metabolites that have been conjugated with glucuronic acid glycine or *sulfate*. Acidic drugs such as chlorthiazide salicylic acid penicillin and acetylated sulfonamides share this system which is the same or similar to the tubular reabsorption system for uric acid This explains why these drugs and other acidic diuretics may cause hyperuricemia. Basic drugs are secreted by another specific, energy dependent system In newborn and especially in premature infants, these renal tubular secretory mechanisms are inefficient and underdeveloped permitting rapid accumulation of excessive drug levels unless the dose is modified Drugs may also compete with each other for the tubular secretory process, which explains the potentiation of isoniazid by aminosalicylic acid

In vitro interactions—the other side

Drugs may still interact adversely even after they have left the patient by confounding the interpretation of laboratory tests. Such an *example is the false* positive increase in urinary 5 hydroxyindoleacetic acid (5 HIAA) caused by a metabolite of the expectorant glyceryl guaiacolate. This may lead to confusion during evaluation of patients for the carcinoid syndrome especially since patients with asthma commonly take a regimen of medications which contain this preparation

Modification of drug handling by disease

The handling of drugs can be dramatically modified by disease. While it has long been appreciated that severe liver or renal

. Downs, A. R., and Morrow I. M Valvular stenoses in vein grafts, Curr Top. Surg Res. 1:499 1969.
. Breslau, R. C. and DeWeese, J A.: Successful endophlebectomy of autogenous venous bypass graft, Ann. Surg 162:251, 1965.
10. McNamara, J D Darling, R. C., and Linton R. R.: Segmental stenosis of saphenous-vein autografts. Preventable cause of late occlusion in arterial reconstruction, New Eng. J Med 277:290, 1967

Potentially dangerous rate and amplitude control interaction in an external battery powered demand pacemaker

Certain new applications for electronic pacemaking of the heart make it mandatory that such devices perform in accordance with published specifications. Because of our interest in the overdrive technique for control of arrhythmias, we frequently utilize external pacemakers t rates of stimulation over 100 per minute. Recently have had occasion to test the Medtronics Model 5840 external demand pacemaker at rates of stimulation above 100 per minute. Specifications furnished by the manufac turer (Medtronics, Inc., 3055 Old High ay Eight, Minneapolis, Minn. 55418) indicate pacing rates from 50 to 150 pulses per minute and an output control capable of adjusting the amplitude from 0 5 to 25 Ma. No mention is made of interaction between the controls Although recent issue of *Medtronic News*[a] states that this instrument was designed to be used with the Medtronic 5821 endocardial electrode, this pacemaker is commonly used ith pacing catheters supplied by other manufacturers W have found that although this unit is reliable for rapid rates of stimulation at low-amplitude settings, the rate acutely drops and pacing is intermittent when the amplitude is raised above limit hich varies with the individual pacemaker This characteristic of the Medtronics Model 5840 makes it unsuitable and indeed dangerous for all applications requiring rapid rate of stimulation in patient ith high threshold

Our discovery of this phenomenon occurred during treatment of 54-year-old woman with intermittent sinus bradycardia and episodes of sinoatrial and trioventricular block punctuated by runs of entricular tachycardia. Because of this, 5 F Goetz transvenous bipolar pacemaker catheter (U S. Catheter and Instrument Corp., Glens Falls, N Y.) was inserted and pacing at a rate of 100 per minute was begun. The ventricular arrhythmia was suppressed and over period of several eeks her sinus rate speeded up to 70 per minute and sinoatrial and atrioventricular conduction ere re-established. The pacemaker was placed in the demand mode at rate below 70 per minute and she did all. During routine test of the pacemaker it was discovered that pacing at rate of 100 per minute could not be accomplished at high milliamperage when the pacemaker was set in the demand mode. Fig. 1 demonstrates this phenomenon. I A, three sinus beats at rate 83 are noted. The pacemaker is then turned on at 100 per minute at 0.5 Ma. output. I the following trips, the rate is held constant but the amplitude is gradually increased. When the amplitude reaches 12 Ma. (*F*) the pacemaker suddenly begins to function intermittently at a rate of 63 per minute. No escape beats are noted. I *G* the milliamperage is set at 25 which is the maximum output of this unit, and the intermittent pacemaker output continues. Escape sinus beats are now present because of the long pacing interval.

In an ttempt to determine whether this was pacemaker malfunction or an intrinsic defect in design, new battery was inserted into the pacemaker but pacing as still intermittent at rate of 100 or more with 12 Ma. or higher output. Three other Model 5840 pacemakers were substituted for the original one and all demonstrated the same defect at high output levels. One of these, set at rate of 80 per minute, intermittently reverted to 60 per minute when the amplitude was raised above 12 Ma. Pacing was maintained, however when any of the units was shifted to the standard pace (fixed-rate) mode.

Each of the pacemakers was connected to resistors of varying values from 47 ohms to 15 meg ohms. I no instance could this phenomenon be demonstrated. However when a pacemaker was attached to a 5 F Goetz bipolar electrode catheter with the electrodes immersed in bottle of 0.9 per cent saline, the pacing became intermittent in the demand mode at high outputs with certain configurations of the catheter The resistance of this system was found to be about 5 K-ohms using a Simpson VOM instrument, but substitution of a 5 K-ohm resistor across the output terminals of the pacemaker for this system did not produce intermittent pacemaker output. Since direct current must be passed through a circuit to determine its resistance, no attempt was made to determine the resistance of the electrode catheter in the patient' heart.

From these tests we conclude that there is an intrinsic design defect in this unit that causes it to stimulate intermittently at high output levels. This

Assessment of reconstructive procedures for femoropopliteal artery occlusive disease

The purpose of this study is to review our experience with femoropopliteal artery reconstructive procedures in an attempt to ascertain the method of choice From June 1957 to June 1967 117 femoropopliteal reconstructions were performed in 105 extremities of 101 patients. Males outnumbered females 9 to 1 Eighty four per cent of the patients were over 50 years of age and 80 per cent had additional manifestations of arterial disease. Diabetes mellitus was present in 18 per cent.

The indications for operation were claudication in 46 extremities rest pain in 41 and ischemic ulceration or gangrene in 18 Preoperative angiography was performed in all patients to assess the inflow outflow and extent of the blockage in the femoral system. The popliteal outflow was considered good or excellent in 76 extremities and fair or poor in 36. Arterial homografts were used prior to 1958. Synthetic grafts were used from 1958 to 1961 Since 1961 reversed autogenous saphenous vein grafts and thromboendarterectomy have been used almost entirely Thirty-one patients have had concomitant lumbar sympathectomy usually when rest pain or gangrene were present.

There were three postoperative deaths, two due to gram-negative septicemia and one due to liver failure. Leg edema is common following these operations and occurred in 29 patients. Twenty three patients developed wound complications the majority of which were superficial skin necroses associated with a long thigh incision for removal of the saphenous vein. Fifteen patients developed pulmonary complications. Two patients developed coronary insufficiency postoperatively

Follow up examination has been completed by the attending surgeon in most instances. Postoperative arteriograms have been done in 49 patients. Fifteen of the twenty-one deaths in the follow-up period were due to arteriosclerotic cardiovascular disease.

All of the homografts have occluded. Synthetic grafts have given relatively poor late results with 40 per cent of the Dacron grafts and 33 per cent of the Teflon grafts remaining patent. Although the early results with thromboendarterectomy were good the late patency rate of 50 per cent has been disappointing The reversed autogenous saphenous vein grafts have given the best results with an early success rate of 90 per cent and a late success rate of 76 per cent. Most of the vein-graft occlusions have occurred within 24 months of operation. Of 41 grafts at risk over 2 years, none have occluded. It is apparent that the long term patency rate is related to the adequacy of the popliteal outflow tract Of the 13 postoperative occlusions 7 have been reoperated on successfully The amputation rate for the entire series was 13.3 per cent and for the graft occlusion group 27 4 per cent. Three patients have developed vein-graft stenosis, and two of these have been successfully repaired. It is apparent that these stenoses are due to valve fibrosis in the graft.[1-4] In support of the findings of other authors[1-] our own results indicate that reversed autogenous saphenous vein graft is the preferred procedure for femoropopliteal artery reconstruction.

Allan R. Downs M.D F.R.C.S (C) F.A C.S.
Associate Professor of Surgery
University of Manitoba
700 William Ave.
Winnipeg 3 Manitoba

REFERENCES

1 Linton R. R. and Darling, R. C. Autogenous saphenous vein bypass grafts in femoropopliteal obliterative arterial disease, Surgery 51:62 1962.
2 Kunlin J Rev Chir (Paris) 0:206, 1951.
3 Darling R. C Linton, R. R. and Razzuk, M A. Saphenous vein bypass grafts for femoropopliteal occlusive disease: A reappraisal, Surgery 61:31 1967
4 Gutelius, J R. Kreindler S., and Luke, J C.: Comparative evaluation of autogenous vein bypass graft and endarterectomy in superficial femoral artery reconstruction, Surgery 57:28 1965.
5 DeWeese, J A. Terry R. Barner H. and Rob, C. G.: Autogenous venous femoropopliteal bypass grafts, Surgery 59:28, 1966.
6. Vollmar J Trede, M Laubach K. and Forrest, H. Principles of reconstructive procedures for chronic femoro-popliteal occlusions. Report on 546 operations, Ann. Surg 168:215 1968.
7 Litherland, H K. and Elliott, J A.: Femoro-popliteal arterial occlusive disease. report of 180 autogenous vein by-pass grafts, Canad. J Surg. 10 186, 1967

8. Dowsm, A. R., and Morrow L. M. Valvular stenoses in vein grafts, Curr Top. Surg. Res. 1:499 1969
9. Breslau, R. C., and DeWeese, J. A.: Successful endophlebectomy of autogenous venous bypass graft, Ann. Surg 162:251 1965.
10. McNamara, J. D., Darling, R. C., and Linton, R. R.: Segmental stenosis of saphenous-vein autografts. Preventable cause of late occlusion in arterial reconstruction, New Eng. J. Med. 277:290, 1967

Potentially dangerous rate and amplitude control interaction in an external battery powered demand pacemaker

Certain new applications for electronic pacemaking of the heart make it mandatory that such devices *perform in accordance with published specifications.* Because of our interest in the overdrive technique for control of arrhythmias, frequently utilize external pacemakers at rates of stimulation over 100 per minute. Recently we have had occasion to test the Medtronic Model 5840 external demand pacemaker at rates of stimulation above 100 per minute. *Specifications furnished by the manufacturer* (Medtronic, Inc., 3055 Old Highway Eight, Minneapolis, Minn. 55418) indicate pacing rates from 50 to 150 pulses per minute and an output control capable of adjusting the amplitude from 0.5 to 25 Ma. N mention is made of interaction between the controls. Although a recent issue of *Medtronic News* states that *this instrument as designed to be used* ith the Medtronic 5821 endocardial electrode, this pacemaker is commonly used ith pacing catheters supplied by other manufacturers. W have found that although this unit is reliable for rapid rates of stimulation at low-amplitude settings, the rate acutely drops and pacing is intermittent when the amplitude is raised above *limit hich varies ith* the individual pacemaker. This characteristic of the Medtronic Model 5840 makes it unsuitable and indeed dangerous for all applications requiring *rapid rate* of stimulation in patient with high threshold.

Our discovery of this phenomenon occurred during treatment of 54-year-old *oman with intermittent* sinus bradycardia and episodes of sinoatrial and atrioventricular block punctuated by runs of ventricular tachycardia. Because of this, a 5 F Goetz transvenous bipolar pacemaker catheter (U. S. Catheter and Instrument Corp Glens Falls, N Y) as inserted and pacing at rate of 100 per minute as begun. The ventricular arrhythmia was suppressed and over period of several weeks her sinus rate speeded up to 70 per minute and sinoatrial and atrioventricular conduction were re-established. The pacemaker *as placed* in the demand mode at rate below 70 per minute and she did ell. During routine test of the pacemaker it was discovered that pacing at rate of 100 per minute could not be accomplished t high milliamperage when the pacemaker was set in the demand mode. Fig. 1 demonstrates this phenomenon. In *A* three sinus beats at rate 83 are noted. The pacemaker is then turned on at 100 per minute t 0.5 Ma. output. In the following strips, the rate is held constant but the amplitude is gradually increased. When the amplitude reaches 12 Ma. (*F*) the pacemaker suddenly begins to function intermittently at a rate of 63 per min te. N escape beats are noted. In *G* the *milliamperage* is set at 25 which is the maximum output of this unit, and the intermittent pacemaker output continues. Escape sinus beats are now present because of the long pacing interval.

I an ttempt to determine whether this was a pacemaker malfunction or an intrinsic defect in design, new battery was inserted into the pace*maker but pacing as still intermittent at rate of* 100 or more with 12 Ma. or higher output. Three other Model 5840 pacemakers were substituted for the original one and all demonstrated the same defect at high *output* levels. One of these, set t rate of 80 per minute, intermittently reverted to 60 per minute when the amplitude was raised abov 12 Ma. Pacing was maintained, however when any of the units was shifted to the standard pace (fixed-rate) mode.

Each of the pacemakers was connected to resistors of arying values from 47 ohms to 15 meg ohms. In no instance could this phenomenon be demonstrated. However when a pacemaker was *ttached to a 5 F Goetz bipolar electrode catheter* with the electrodes immersed in a bottle of 0.9 per cent saline, the pacing became intermittent in the demand mode t high outputs with certain configurations of the catheter. The resistance of this system was found to be about 5 K-ohms using a Simpson VOM instrument, but substitution of a *5 K-ohm resistor* across the output terminals of the pacemaker for this system did not produce intermittent pacemaker output. Since direct current must be passed through circuit to determine its resistance, no ttempt was made to determine the resistance of the electrode catheter in the patient heart.

From these tests e conclude that there is an *intrinsic design defect in this unit* that causes it to stimulate intermittently at high output levels. This

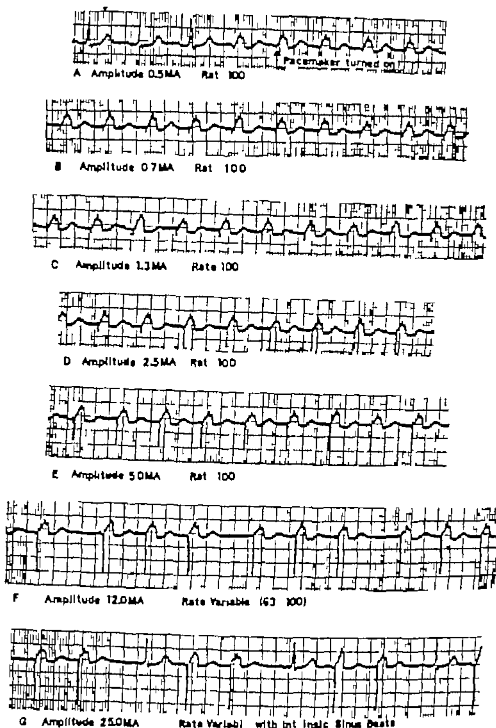


Fig 1 ECG tracings with pacemaker set at various amplitudes.

defect is apparently in the pulse detection or demand function circuitry since it cannot be demonstrated unless the demand mode of paci g is used and the unit is connected to a pacing catheter Standard electronic bench test ng would probably not re eal this potential hazard. This defect makes such u ts unsuitable for any application in which demand pacing at a high stimulation rate is required and the patient has a high pacing threshold. Two such applications would include rapid pacing for suppression of ventricular arrhythmias in a patient with myocardial infarction or atrial pacing which often req ires h gh illiamperage because of intermittent floating of the catheter in the trium. Although we have not experimented with batteries in a partially discharged condition, it is conceivable that these units powered by such cells might even malfunction at lower rates of stimulation or output current, making them unsuitable for all demand applications.

The manufacturers ha e been informed of our difficulties with these pacemakers and seemed to be aware of the problem. They have offered t modify each of them so as to eliminate the defect. It is felt,

however that wide arenes of this problem may prevent pacemaker malfunctions which could endanger the lives of patients.

Barry M Beller M.D
Giovanni P pulle, M.D
Department of Physiology nd Medicine
The U versity of Texas Medical School
at San Antonio
7703 Floyd Curl Drv
San Antonio, Texas 78229

REFERENCES

1. Beller B., Frater R. W and Wolfsohn, N t Cardiac pacemaking in the management of post operative arrhythmias, Ann. Thorac. Surg 6:68 1968.
2. Beller B Kotler M N and Collens, R.: Suppression of ectopic entricular activity by cardiac pacing, Amer J Cardiol. 25:167 1970.
3. Notes on successful pplication of the Model 5840 demand pacemaker Medtronics New 1:3, 1969

Paroxysmal cough induced by transvenous pacemaker

Transvenous endocardial pacing, first introduced by Furman and Robinson[1] in 1958 has become the method of choice in recent years for both temporary and permanent pacing. The complications reported from this form of pacing include wire breakage, electrode displacement myocardial penetration and perforation pulse generator failure, including run-y pacemaker and cessation of pacing wound infection septicemia; pulse generator extrusion pulmonary embolism from thrombus formation on the catheter pulmonary air embolus during insertion diaphragmatic stimulation; and epilepsy An additional complication, to our knowledge not reported previously namely paroxysmal cough induced by temporary transvenous pacing is the subject of this report. The patient is 75-year-old Caucasian oman ho as admitted to the Intensi Care Unit of Queens Hospital Center for acute anteroseptal myocardial infarction. The patient demonstrated sinus bradycardia t the rate of 45 to 50/min with occasional episodes of sinoatrial block. When it as determined that satisfactory heart rate could not be maintained ith intravenous atropine, transvenous pacing catheter as inserted percutaneously through the right femoral ein and advanced into the apex of the right ventricle and connected to demand type pulse unit. It as noted that as soon as the heart as paced the patient began to cough. The cough as quite bothersome to the patient so that the unit had to be turned off, but each time the pacemaker as turned on the cough recurred and the pacing had to be discontinued. The position of the pacing electrode was rechecked fluoroscopically and seemed to be in good position in the apex of the right entricle furthermore, no diaphragmatic movements produced by pacemaker stimuli ere noted. The pacing threshold as reduced to 1.5 Ma., but coughing persisted; below 1.5 Ma. both effecti pacing and coughing ceased. At thresholds of 1.5 Ma and above both cough and adequate pacing recurred despite hanging the electrode position to various regions of the ventricle including both inflow and outflow tracts. When the pacemaker was withdra into the right atrium, effective pacing was also accomplished but the cough persisted. The pacing catheter was then removed and new pacemaker catheter was inserted through the left femoral ein int the right entricular apex only to reproduce the same events. It was noted that when the pacing electrode was in the inferior vena cava neither effecti pacing nor coughing ensued. Because the cough was so bothersome to the patient, the pacemaker was then left in adequate position in the right ventricular pex but turned off. The temporary pacing catheter was then removed 10 days later after normal sinus rhythm was restored. On the tenth hospital day just prior to the removal of the pacing catheter pneumograph and an electrocardiograph were recorded simultaneously during pacing and without pacing (Fig. 1)

The cough reflex is complex one normally initiated by irritation of nerve endings in arious locations, transmitted by afferent nerves to the cough center located in the dorsolateral region of the medulla at the level of the olivary bodies and adjacent to the rootlets of the vagus and glossopharyngeal nerve[2] and mediated by efferent nerves to the glottis, tracheobronchial trees, intercostal and abdominal muscles as well as the diaphragm. The know afferent path y of the cough reflex are as follows[3]: (1) from the external meatus of the ear through Arnold' nerv (auricular branch of the vagus) (2) from the pharynx through the glossopharyngeal and pharyngeal branch of the vagus (3) from the larynx through the superior laryngeal branch of the vagus (4) from the trachea, bronchi, and pleura through the pulmonary branches of the vagus (5) from the diaphragm through the cardiac and esophageal branches of the vagus (6) and from

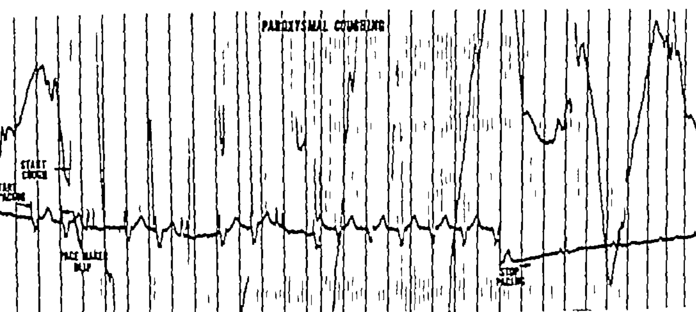


Fig 1 Simultaneous ECG and pneumograph Note change in pneumograph produced by coughing beginning after second pacemaker beat and ending when pacing was discontinued

the pericardium through the phrenic nerve In our patient it is possible that the electrical pacemaker stimulated afferent nerve endings either in the diaphragm or in the pericardium since these endings appear to be in closest proximity to our pacing electrode and possibly an abnormally low threshold peculiar to this patient is responsible for initiating the reflex. Another theoretical consideration of which we know of no precedent is that anomalous vagal nerve endings may be present in the endomyocardium of this patient which are responsible for initiation of the cough reflex

Jagu Kang M.D
Mohinder Gupta M.D
Pablo 1 Catangay M D
Francis Raia M D

From the Department of Medicine
Cardiopulmonary Laboratory
The Long Island Jewish Hospital and
Mary Immaculate Hospital
Queens Hospital Center Affiliation
Queens, N Y 11432

REFERENCES

1 Furman S. and Robinson G. The use of an intracardiac pacemaker in correction of total heart block, Surg Forum 9 745, 1958.
2 Harris, A. M Endocardial pacing AMER. HEART J 72:135 1966.
3 Bickman H A. Bronchial drainage and phenomena of cough in Clinical cardiopulmonary physiology New York, 1960, Grune & Stratton, Inc. p 500.

An association between the billowing posterior mitral leaflet syndrome and congenital heart disease, particularly atrial septal defect

Early studies[1-4] of subjects with a late systolic murmur or nonejection click, either of which probably always denotes billowing of the posterior mitral leaflet[5-8] revealed 4 patients, each with an isolated nonejection click who had an associated atrial septal defect of the secundum type. A thickened chorda tendinea to the posterior leaflet was palpated in one patient and in another the edges of the mitral leaflets were thought by the surgeon to be thickened.[1,4] No abnormality of the mitral valve was detected in the remaining 2 patients.[3] The systolic click remained in each instance after the septal defect had been closed.

A recent analysis of 200 patients with a late systolic murmur a nonejection click, or both revealed that 17 including the 2 reported previously[3] had an associated secundum atrial septal defect. With the exception of a 4-year-old boy all were female patients with an age range from 6 to 59 years. The septal defect has been closed in all but 3 pa-

tients, 2 of hom have an isolated nonejection click and the third, late systolic murmur and nonejection click. Isolated nonejection clicks, present in 3 patients preoperatively disappeared in each instance after closure of the septal defect, whereas in 2 others the auscultatory signs of mitral valve pathology ere heard for the first time postoperatively; both developed late systolic murmur and one developed nonejection click as well. Three patients had nonejection click before and after operation. Five patients had varying combinations of late systolic murmur and nonejection click before and after surgery. The last patient, 22 year old oman, had Grade II pansystolic murmur preoperatively and mild mitral regurgitation was confirmed on left ventricular angiography but, since operation, the systolic murmur has been confined to late systole and a nonejection click has appeared.

The surgeon endeavored to assess the anatomy of the mitral leaflets and chordae in 11 of the 14 patients subjected to surgery. Apart from the 2 already mentioned,[1,3] valve abnormality was detected in only 2, one of whom was the 22 year-old oman ho had had pansystolic murmur preoperatively. The chordae to her posterior leaflet were thickened and shortened and are regarded by the surgeon as compatible with rheumatic involvement. The other patient was a 7 year-old girl ith late systolic murmur and nonejection click, both leaflets of her mitral valv were voluminous and one chorda tendinea to the anterior leaflet had ruptured. Because of limited access during closure of an trial septal defect, detailed inspection and palpation of the mitral chordae are difficult and ould increase the risk of air embolism. It is thus understandable that no definite pathology was detected in the remaining 7 patients. One of these, a 9-year-old girl, has subsequently developed presystolic and mid-diastolic mitral murmurs, whereas her late systolic murmur and systolic click are no longer udible. Since this patient has history of recurrent joint pains and her mother has had mitral commissurotomy the cause of her late systolic murmur and click may ell have been rheumatic. It is noteworthy that one of the 3 patients who have not yet been subjected to surgery is her 8-year-old sister ho has late systolic murmur and click. I remains possible that the three separate entities of secundum trial septal defect, the billowing posterior mitral leaflet syndrome, and heumatic endocarditis are prevalent in this family.

The atrial septal defect, as assessed clinically by catheterization or at surgery was large in all 17 patients. I the 14 subjected to surgery the defect as of typical secundum type, situated posteriorly and ell y from the anteriorly placed mitral valve. It thus seems unlikely that the defect could directly affect either the anatomy or function of the mitral valve, and it ould appear that valid organic disease of the mitral leaflets or chordae is separate entity.

Chest pain, usually atypical for angina, is not infrequent symptom in patients with the billowing posterior mitral leaflet syndrome.[1,4,8,7-9] Only one of the 17 patients complained of chest pain. This as the 22 year-old oman ho had thickened chordae, possibly on a rheumatic basis, to the posterior leaflet. During routine follow-up visit three years after her operation, she volunteered that she had experienced 3 recent episodes of fairly severe chest pain, lasting from one-half to te minutes, which radiated dow her left arm and was accompanied by sweating. Apart from residual rSr' pattern, her electrocardiogram was normal t rest nd no premature ventricular contractions developed after strenuous effort.[10]

There are 5 patients with other forms of congenital heart disease I our series of 200 cases. These comprise 23-year-old man with Eisenmenger syndrome due to ventricular septal defect ho has 2 nonejection systolic clicks 2 girls, aged 12 and 14 years, respectively with an inoperable patent ductus arteriosus, both of hom have late systolic murmur and nonejection click, and 2 young women, previously reported,[1,9] each ith nonejection systolic click present before and after a patent ductus arteriosus was ligated.

It would appear that the association of congenital heart disease, particularly secundum trial septal defect, and late systolic murmurs and nonejection clicks is greater than can be accounted for by chance. Although not yet understood on an embryological basis, developmental abnormality of the mitral valve is likely in many instances. However coincidental rheumatic endocarditis, papillary muscle dysfunction caused by mild associated fibroelastosis or functional effect on the mitral valve mechanism, by the atrial septal defect, may all prove to be factors in some instances. Irrespectiv of the cause or nature of the mitral valve pathology it is important to be are of this association since prophy laxis against bacterial endocarditis, an extremely rare complication of secundum trial septal defect, is indicated in patients with the billowing posterior mitral leaflet syndrome.[12-14]

Wendy A. Pocock, M.B. M.R.C.P.
John B. Barlow M.D. M.R.C.P.
South African M.R.C.
Cardiovascular Research Unit
Department of Medicine
University of the Witwatersrand
Johannesburg, South Africa

REFERENCES

1. Barlow J. B., Conjoint clinic on the clinical significance of late systolic murmurs and nonejection systolic clicks, J. Chronic Dis. 18:665 1965.
2. Hancock, E. W. and Cohn, K.: The syndrome associated with midsystolic click and late systolic murmur Amer J. Med. 41 183, 1966.
3. Barlow J. B., Bosman, C. K., Pocock, W. A. and Marchand, P.. Late systolic murmurs and nonejection ("mid-late") systolic clicks. An analysis of 90 patients, Brit. Heart J. 30:203 1968.
4. Criley J. M., Lewis, K. B., Humphries, J. O. and Ross, R. S.: Prolapse of the mitral valve: clinical and cine-angiocardiographic findings, Brit. Heart J. 28:488, 1966.
5. Stannard, M., Sloman, J. G., Hare, W. S. C., and Goble, A. J.: Prolapse of the posterior

leaflet of the mitral valve. A clinical familial and cine-angiographic study Brit. Med. J 3:71 1967
6. Pocock, W A., and Barlow J B : (In preparation.)
7 Tavel M E. Campbell, R. W and Zimmer J F Late systolic murmurs and mitral regurgitation Amer J Cardiol. 15:719 1965
8. Barlow J B and Bosman, C K. Aneurysmal protrusion of the posterior leaflet of the mitral valve, Amer. Heart J 1:166, 1966.
9 Shell, W E. Walton J A. Clifford M E. and Willis, P W The familial occurrence of the syndrome of mid late systolic click and late systolic murmur Circulation 39:327 1969
10 Barlow J B. and Pocock, W A: The effort electrocardiogram in the billowing posterior mitral leaflet syndrome, Circulation 40: Suppl. III-40, 1969 (Abst.)
11 Pocock, W A. and Barlow J B. Post-exercise arrhythmias in the billowing posterior mitral leaflet syndrome, Amer. Heart J (In press.)
12. Facquet, J., Alhomme, P and Raharison, S. Sur la signification du souffle fréquemment associé au claquement télésystolique, Acta Cardiol. (Brux.) 19:417 1964.
13. Linhart, J W and Taylor W J The late apical systolic murmur Clinical, hemodynamic and angiographic observations, Amer J Cardiol. 18:164 1966.
14. Lo Bauer E. J Perloff J K. and Keliber T F : The isolated systolic click with bacterial endocarditis. Case report, Amer. Heart J 73:534 1967

Letters to the Editor

Cardiac pacing in acute myocardial infarction complicated by complete heart block

To the Editor:

Schluger, Iraj, and Edson are to be congratulated for their excellent review on cardiac pacing in complete heart block complicating myocardial infarction (AMERICAN HEART JOURNAL, July 1970). Unfortunately, referring to their description of the influence of QRS morphology on the development of complete heart block, they fail to mention the excellent and recent work of Godman and associates, who showed that, in 68 patients with bundle branch block complicating acute myocardial infarction, 21 (31 per cent) went on to develop complete heart block. There were 48 patients with right bundle branch block and 15 developed complete heart block. The remaining 20 patients had left bundle branch block and six developed complete heart block. Analyzing the figures further they showed that 47 patients had "unilateral" bundle branch block and six developed complete heart block and the rest, i.e., 21 patients had "bilateral" bundle branch block and 15 developed complete heart block. Prophylactic introduction of pacemaker was done in 31 patients with bundle branch block. Nine of these patients went on to develop complete heart block and were paced with no reduction in mortality rates.

Definitive and concrete answers on the use of pacemaker treatment in acute myocardial infarction, especially with complete heart block, will be forthcoming only after a large careful and controlled series, preferably on a national scale.

Abdul H. Khan, M.D.
Fellow in Cardiology
St. Francis Hospital
Hartford, Conn.

REFERENCE

1. Godman, M. J., Lassers, B. W., and Julian, D. G.: Complete heart block complicating acute myocardial infarction, New Eng. J. Med. 282:237, 1970.

Reply

To the Editor:

We thank Dr. Khan for his kind comment. The report by Godman and his group was not published until after we had completed our review. We were most interested in this report, however, since it tends to confirm the conclusions drawn from our review. It appears that even the prophylactic introduction of pacemaker catheters and early pacing have little effect on the deaths resulting from myocardial infarction complicated by complete heart block.

Joseph Schluger, M.D.
Iraj Iraj, M.D.
John N. Edson, M.D.
Cardiac Catheterization Laboratory
The Long Island College Hospital
Brooklyn, N. Y.

Mortality rates with cardiac pacing in acute myocardial infarction

To the Editor:

In a recent review Schluger, Iraj, and Edson[1] state that the optimum improvement in mortality rate with the employment of cardiac pacing in acute myocardial infarction complicated by complete heart block represents a possible salvage of 1,200 to 1,600 lives annually. This is considerably lower than the 10,000 to 15,000 saving in lives previously estimated editorially (in J.A.M.A.).[2]

I should like to point out that, in a communication published in the same year and in the same journal as the original editorial, I indicated that a more realistic figure would be a saving of 1,500 to 2,000 lives annually.[3] Interestingly enough, my calculations included several factors not considered by Schluger and colleagues. If one considers all arguments as noted in both of our reports, the salvage figure with pacing might reasonably be reduced to *less than* 1,000 lives annually.

Philip I. Hershberg, M.D.
Department of Physiology
School of Public Health
Harvard University
Boston, Mass.

REFERENCES

1. Schluger, J., Iraj, I., and Edson, J. N.: Cardiac pacing in acute myocardial infarction complicated by heart block, AMER. HEART J. 80:116, 1970.
2. Editorial: Cardiac pacing and acute heart block, J.A.M.A. 203:356, 1968.
3. Hershberg, P. I.: Salvage from myocardial infarction, J.A.M.A. 205:484, 1968.

Reply

To the Editor:

We were unaware of Dr. Hershberg's Letter to the Editor in the Journal of the American Medical

leaflet of the mitral valve. A clinical, familial and cine-angiographic study Brit. Med. J 3:71 1967
6 Pocock W A. and Barlow J B (In preparation.)
7 Tavel, M E. Campbell R. W and Zimmer J F Late systolic murmurs and mitral regurgitation, Amer J Cardiol. 15:719 1965
8. Barlow J B and Bosman, C. K. Aneurysmal protrusion of the posterior leaflet of the mitral valve, AMER. HEART J 71:166 1966.
9 Shell W E Walton J A. Clifford M E. and Willis, P W The familial occurrence of the syndrome of mid late systolic click and late systolic murmur Circulation 39:327 1969
10 Barlow J B and Pocock, W A. The effort electrocardiogram in the billowing posterior mitral leaflet syndrome, Circulation 40: Suppl. III-40 1969 (Abst.)
11 Pocock, W A. and Barlow J B : Post-exercise arrhythmias in the billowing posterior mitral leaflet syndrome, AMER. HEART J (In press.)
12. Facquet, J Alhomme, P and Raharison, S. Sur la signification du souffle fréquemment associé au claquement télésystolique, Acta Cardiol. (Brux.) 19:417 1964.
13. Linhart J W., and Taylor W J The late apical systolic murmur Clinical hemodynamic and angiographic observations, Amer J Cardiol. 18:164 1966.
14 Le Bauer E. J Perloff J K., and Keliher T F The isolated systolic click with bacterial endocarditis. Case report AMER. HEART J 73:534 1967

Diagnosis of posterior infarction

To the Editor

I read with interest the clinical p thologic conference (AMER. HEA T J 80:562 1970) i which Prof. Shillingford analyzes the unusual case in a splendid y Nevertheless, I was confused by the diagnosis of posterior infarction in the presence of manifest Q wave with negati T w I Leads II, III, and V$_F$ which, in electrocardiogr phy means classical inferior all infarction (par diaphragmatica cordis). Posterior infarction is characterized on the ECG by tall R w es and T w ves in V and V and in the horizontal projection of the ectorcardiogram by the 45 msec vector situated anteriorly and the maximal anterior Z orthogonal greater tha the maximal posterior Z component. Vectorcardiographically inferior nfarction is determined by clock se superior loop of t least 25 msec. in the frontal projection. Some authors have called posterior infarction, t differentiate it from inferior infarction, "true posterior infarction. I believe this is superfluous because it may suggest that other infarctions are not true

Anatomically posterior wall nfarction is the opposite of anterior all infarction of the left entricle the opposite of inferior all infarction, if such there be, should be left atrial infarction.

Of course, this correction of nomenclature does not change the logic of Prof Shillingford analysis. Although Shakespeare[2] rote, What in name?" must clarify this nomenclature now for us, for our colleagues, and for our students.

Koen J J Bruyneel, M.D
Cardiac Cli ic
U ersity of Ghent
Ghent Belgium

REFERENCES

1. Bruschke, A. V G. The diagnostic significance of the coronary arteriogram, Thesis, 1969, Groningen, The Netherlands
2. Shakespeare, W Romeo and Juliette, 2:2.

*Present address: Groote Schuur Hospital, Cardiac clinic, Observatory Cape Town, South Africa.

Reply

To the Editor

Thank you for your letter and the copy of the one from Dr Bruyneel. He is, of course, right and "posterior" should read "inferior I must apologize for any confusion so caused. At the same time I should like to thank Dr. Bruyneel for pointing out the mistake in the text.

J P Shillingford
Royal Postgraduate Medical School
Hammersmith Hospital
London W12 England

Methods of measurement of mechanical events of the left ventricle

To the Editor

I ha some remarks to make concerning the paper by Drs. S. Kumar and D Spodick, entitled "Study of the mechanical event of the left ventricle by atraumatic techniques Comparison of methods of measurement nd their si nificance (AMER. HEART J 80:401 1970)

I previous paper (AMER. HEART J 76:498, 1968) the same authors d scussed six method for indirect measurement of isovolumetric contraction time (IVCT) and came to the conclusion that (IVCT) and came to the conclusion that Calculation 2, suggested by me ("Indirect measureme t of isovol mic contraction time on the basis of polygr phic tracing, Cardiologia 47:315 1965) appeared t be the optimum method for measuring IVCT by traumatic techniques. In the present paper by Drs. Kumar and Spodick (AMER. HEART J 80:401 19 0, p. 404 second column) the same six methods for indirect measurement of IVCT are discussed in the same order as in the previous paper but the authors of the methods are not mentioned. The reader ould therefore be under the false impression that Drs. Kumar nd Spodick originally suggested these methods. Fi e out of the six papers in question, including mine (Cardiologia 47:315 1965) ere quoted by Drs. Kumar and Spodick, but concerning other problems or matters of secondary importance.

I onder whether you ould care to rectify this situation by publishing a ord in the AMERICAN HEAR JOURNAL. I presume this has been a ery involuntary lapse on the part of my colleagues, Drs. Kumar and Spodick.

Vesselin I Oreshkov M.D
Higher Medical Institute
Sofia 31 Bulgaria

Reply

To the Editor

I our review of atraumatic techniques Dr Kumar and I considered number of methods of determining not only IVCT but LVET IRP RFP and other intervals, including comparati evaluations of them made by us and by others. For IVCT we cited our own comparison of six methods, with no implication of origination by us of any of them. Indeed, applications of noninvasive measurements represent a sy thesis of ork by many investigators, notably Blumberger and others of the German School and later Weissler and Benchimol in the United States and Van Bogaert in Belgium.

With regard to Dr Oreshkov claim, e became ware of his report only during our search of the literature after e began to rite up our completed ork (rarely see copies of *Cardiologia*, Swiss journal) I fact, our stimulus to include the calculation, IVCT = CAR, minus PTT came from the ork of Tafur Cohen, and Levine, published one

Association. We are pleased that there is such close agreement between both estimates of the maximum possible saving of lives resulting from cardiac pacing in acute myocardial infarction complicated by complete heart block. We would agree that consideration of all factors mentioned in Dr Hershberg's letter and our review would tend to further lower the estimates of possible salvage

Joseph Schluger M D
Iraj Iraj M D
John N Edson M D
Cardiac Catheterization Laboratory
The Long Island College Hospital
Brooklyn N Y

Failure of repeated diazoxide injections to modify the course of severe hypertension

To the Editor

The manuscript by Beamer and McDonald, "Failure of repeated diazoxide injections to modify the course of severe hypertension," which appeared in the June 1970, issue of the AMERICAN HEART JOURNAL, clearly demonstrates the complications resulting from the use of antihypertensive agents alone. Since the findings of Beamer and McDonald stand in marked contrast to those reported by us, a comparison of the two protocols seems in order

1 All of Beamer's patients continued to receive other antihypertensive agents while on diazoxide, e.g. guanethidine bethanidine or methyldopa whereas ours received no other antihypertensive agent except for chlorthalidone which was administered in most patients.

2. The arterial pressure was well controlled in 14 of our 16 patients. The arterial pressure was not reduced significantly in four of Beamer's patients

3 When a diuretic was administered to two of Beamer's patients it was given in suboptimal dose (500 mg of chlorothiazide a day or ethacrynic acid twice a week) whereas in our group chlorthalidone was given in a dosage of 100 mg. per day in 14 of the 16 patients.

Recent studies from our laboratory[2] document that the fall in arterial pressure with most antihypertensive agents, particularly diazoxide guanethidine, and methyldopa, is associated with a decrease in urinary output and sodium retention which not only aggravates an already impaired renal circulation but frequently produces congestive heart failure. Serial injections of diazoxide over a ten-day period or the chronic administration of methyldopa guanethidine, or hydralazine over a three-month period have produced expansion of the extracellular fluid volume and a decreased hypotensive response. This development of apparent drug resistance has rapidly been eradicated by the administration of diuretics. In patients with normal renal function thiazide diuretics were capable of decreasing the extracellular fluid volume and returning antihypertensive drug response. In patients with impaired renal function, however more potent diuretics such as furosemide were needed.

Clinical experience attests to the fact that drug resistance develops more commonly in patients receiving antihypertensive agents alone than in patients receiving antihypertensive agents in conjunction with diuretics. Since the concomitant administration of diuretics decreases sodium retention it also prevents the expansion of extracellular fluid and the ultimate development of drug resistance It is interesting to speculate further whether the enhanced therapeutic response observed when diuretics are added to an antihypertensive regimen represents true synergism of action or simply a decrease in extracellular fluid volume. Since an expanded extracellular fluid volume seems to decrease antihypertensive activity and in some patients contributes to the development of drug resistance and since diuretics decrease extracellular fluid volume and can frequently reverse or prevent these phenomena, it would seem that diuretics should be an integral part of all antihypertensive regimens, parenteral as well as oral.

Frank A Finnerty Jr M.D
Professor (Clin.) of Medicine
Professor (Clin.) Obstetrics and Gynecology
Georgetown University Medical Center
Chief Cardiovascular Research
D C General Hospital
Washington D C

REFERENCES

1 Finnerty F A. Jr Davidov M and Kakaviatos, N Hypertensive vascular disease. The long term effect of rapid repeated reductions of arterial pressure with diazoxide Amer J Cardiol. 19:377 1967

2 Finnerty F A. Relationship of extracellular fluid volume to the development of drug resistance in the hypertensive patient AMER. HEART J 81:563 1971

Reply

To the Editor

Dr Finnerty is quite right, our patients did not achieve the desired results he reported with his patients. We reported the cases of these patients as a failure because it was clear that diazoxide *alone* failed to significantly alter the course of our patients' disease. We undertook the study in part because many of our associates believed that Dr Finnerty and his co-workers had demonstrated a unique quality of diazoxide alone.

To propose adding a diuretic to the regimen is to propose an alternative protocol. We are not convinced enough of the uniqueness of daily diazoxide injections to feel that we wish to undertake a combined diuretic-diazoxide study

Robert H McDonald Jr M.D
Department of Medicine
School of Medicine
University of Pittsburgh
Pittsburgh, Pa.

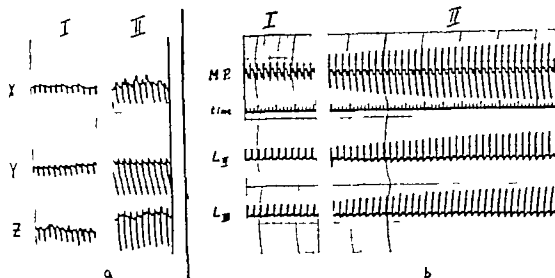


Fig. 1 ECG recordings from turtle before bleeding (*I*) and during bleeding (*II*). Leads X, Y Z, limb Leads L_{II} and L_{III}, and myocardial potential (*M P*) are shown. Time in seconds.

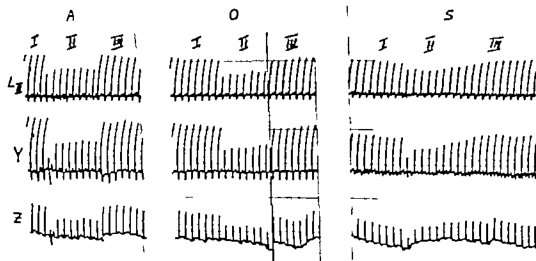


Fig 2 ECG recordings from turtle before (*I*) during (*II*) and after (*III*) intraventricular filling with air (*A*) olive oil (*O*) and Ringer solution (*S*) Leads L_{II}, Y and Z are shown.

tions to bleeding of homeotherms and poikilotherms.

Mordechai Manoach, M.Sc. (Eng.)
Simon Gitter Ph D M.D
Edith Grossman, M Sc.
Daliah Varon, B.Sc.
Department of Physiology and Pharmacology
Medical School
Tel Aviv University
Tel Aviv Israel

REFERENCES

1 Wilson, F N Wishart, S. W and Herrmann, G. R. Factors influencing distribution of potential differences produced by heartbeat t surface of the body Proc. Soc. Exp. Biol. Med. 23:276, 1926.

2. Wilson, F N. The distribution of potential differences produced by the heartbeat within the body and t its surface, Amer. Heart J 5:599 1930.

3. Eyster J A. E Maresh, F and Krasno, M R. The nature of electrical field around the heart, Amer J Physiol. 106:574 1933.

4. Krasno, M. R., Eyster J A. E., and Maaske, C. A. The natur of the T wave potentials in the tortoise heart, Amer J Physiol. 114 113, 1935

year before Dr Oreshkov s[4] paper In a thorough study of the apexcardiogram they indicated that the pre-ejection period should really begin with the ACG upstroke ("ACG in our notation) In a separate study our results for ACG, as a mea ure of electromechanical lag were numerically identical with those of Tafur Cohen, and Levine[3] Wei sler and a sociates and Luisada and Alimurung had already indicated that the end of this interval, i.e the onset of ejection, could be calculated by carotid upstroke (CAR in our notation) minus PTT *Tafur and colleagues,[3] however considered the onset* of ejection to be synchronou with the carotid up- troke which was shown to be erroneou [5] It is to Dr Oreshkov credit that he fir t recognized what we regarded as the correct onset and conclusion of the IVCT

David H Spodick M.D
Associate Professor of Medicine (Cardiology)
Tufts U versity School of Medicine
170 Mort n St
Boston Mass 02130

REFERENCES

1 Kumar S. and Spodick, D H Study of the mechanical events of the left ventricle by atrau matic techniques Comparison of method of measurement and their sig ificance AMER HEART J 80:101 1970
2 Spodick, D H and Kumar S Isovolumic contraction period of the left ventricle AMER. HEART J 76:198 1968
3 Tafur E. Cohen L. S. a d Levine H D The normal apexcardiog am. Its temporal rela tionship to electrical acou tic and mechanical cardiac events, Circulation 30:381 1964
4 Oreshkov V Indirect measurement of isovolumic contraction time on the basi of polygraphic tracing Cardiologia 47:315 1965
5 Spodick D H and Kumar S Electromechani cal lag of the left ventricle Cardiov sc. Res. 2:338 1968
6. Weissler A M Peeler R G and Roehll W H Jr : Relationship between left ventricular ejection time stroke volume and heart rate in normal individuals and patients with cardiovascular disease AMER. HEART J 63:367 1961
7 Luisada A. A. and Alimurung M M *In* Cardiology An encyclopedia of the cardiovascular system New York 1959 McGraw Hill Book Company Inc. vol. 1 pp. 2 92.

Some considerations regarding the importance of blood, heart and tissue conductivity with regard to QRS amplitude changes after hemorrhage

To the Editor

In the last half century amplitude changes of electrocardiographic waves have been examined with regard to the influence of changes in conductivity of the blood the heart, and the surrounding tissues. Several investigators in the field[1-4] related the amplitude of recorded QRS complexes with blood, heart, and lung conductivity Straub[2] and Krasno and associates observed that filling the heart in the frog reduced the amplitude of the ECG while emptying heart in frog and turtle increased the QRS complex. Krasno and his co-workers[3] stated that the greater amplitude of QRS complex in the empty heart compared with that in the heart filled with blood may be due to differences in resistance in shunting circuits inside the heart under these opposite conditions. Eyster and associates postulated that a decrease in body resistance will produce lower voltage of ECG in all leads.

The question arises from the forementioned studies whether this phenomenon really is a function of conductivity or results from the changes in the dimensions and position of the heart.

Our experiments were carried out on frogs (amphibia) turtles, nd lizards (reptilia) ECG was recorded using the three limb leads, X Y and Z as well as a unipolar lead from the ventricular myocardium. Recordings were taken before, during, and after bleed ng or conversely before and after filling of the heart with isotonic Ringer s solution air or ol ve oil The filling was done through the cannulated inferior vena cava or by introducing a cannula directly into the ventricle through the aorta In order t prevent a y changes in the liquid content of the rest of the body during filling of the heart all heart vessels were clamped

During bleed ng the amplitude of QRS complex increased simultaneously in the l mb leads and X Y and Z (Fig 1) This proves that the changes in QRS mplitude are not due to changes of the heart position or rotation of the heart. Moreover the unipolar recordi g from the ventricular myocardium (F g 1 b) lso showed the increased QRS amplitude, which demonstrates that this is a phenomenon of the myocard u itself

Decreased mplitude of the R wave was recorded during fill g of the heart in our experiments when changes in the filling of the lungs or other tissues had been prevented This decrease was recorded in all three l n b leads, X Y nd Z (F g 2) as well as on the myocardium tself during filling regardless of whether Ringer' solution (*S*) air (*A*) or olive oil (*O*) had been used. The pecific resistance of Ringer s sol tion is similar to that of blood, while oli e oil and ir have by comparison a very high resistance. The fact that the decreased amplitude of the R w ve occurred by filling the heart even with substances of lower conducting property proves that the phenomenon is not connected with changes of the short circuit i side the heart or of the conductivity of the surrounding tissue.

In ddition, we have been recently able to show that i homeotherms (birds and mammals) bleeding produces a decrease of the QRS amplitude, and filling of the heart an increase of the same. If blood, heart or tissue conductivity were the reason for the observed electrocardiographic changes there should be no reason for a different response to bleeding in homeotherms as compared with poikilotherms.

Further tudies are now in progress which will contribute to the elucidation of the different reac

Experimental myocardial infarction

To the Editor:

The proliferation of models for the production of coronary artery occlusion attests to the interest in and need for an animal model that will permit further *study of the diagnosis, pathogenesis, and treatment* of myocardial infarction and its complications. Techniques employed for the production of experimental artery occlusion include ligation, the injection of necrotizing agents, and both direct and indirect embolization using a variety of materials. A standard method for producing coronary artery occlusion in the dog was first described by Agress and associates and was further refined by Jacobey and colleagues, Gurman and colleagues, and Bloch and colleagues. All infarcted the heart of the closed-chest dog with sized microspheres embolized directly or indirectly into the coronary arteries. Although standardization has been attempted, all of the procedures lack precision, either with respect to the dosage of microspheres or in the failure to deliver the microspheres directly into the vasculature without spill-over into the systemic circulation. Recently we produced myocardial infarction in 18 anesthetized adult mongrel dogs by passing the catheter under fluoroscopic control and during electrocardiographic monitoring from the left femoral artery into the left coronary artery. Catheter tip placement was verified by a test injection of contrast material. Lidocaine (40 mg.) was administered intravenously just before and just after embolization to minimize the incidence of acute arrhythmias. Left coronary artery embolization was accomplished by the injection of 0.05 mg. per gram of estimated heart weight of Dowex resin microspheres, 297 to 350 μ in diameter. The microspheres, suspended in 5 ml. of 10 per cent low molecular weight dextran, were injected rapidly followed by a saline flush. The control animals were treated in the same fashion with the exception that the bolus of dextran injected into the left coronary artery did not contain the microspheres. Six of the 18 embolized dogs died in the first 30 minutes after embolization of ventricular fibrillation.

Blood samples were collected at frequent intervals in both the 12 surviving embolized dogs and in the 12 control dogs for analysis of serum creatine phosphokinase (CPK) and glutamic oxalacetic transaminase (GOT). Electrocardiograms were taken on alternate days during the first week and weekly thereafter for a period of 30 to 66 days. The animals were then killed and a complete postmortem examination was performed with myocardial tissue preserved for microscopic examination.

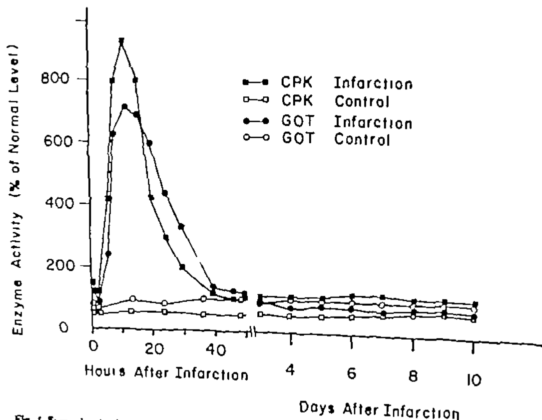


Fig. 1. Serum levels of creatine phosphokinase and GOT at various times after induction of myocardial infarction. Normal serum CPK levels in these studies were approximately 20 units per milliliter of serum and GOT levels were approximately 50 units per milliliter of serum.

5. Straub, H Zur Analyse des Elektrokardiogramms nach Versuchen am isolierten Srosch herzens, Z Biol 53:499 1910
6. Manoach M Gitter S Crossman E, Varon D and Gassner S. The influence of hemorrhage on the QRS complex of the electrocardiogram AMER HEART J In press.

Circulation time and venous pressure

To the Editor

Doctor Selzer in his annotation Circulation time and venous pressure Routine tests?' (AMER. HEART J 80:142 19 0) discouraged the use of these procedures because of limited reliability and low sensitivity

On the contrary we encourage their use in hospital practice to stimulate precise thinking about hemodynamics in just the sort of terms used by Doctor Selzer in his discussion I would like to comment particularly on venous pressure measurements.

It is true that peripheral pres ures may be affected by venou valves and venous spa m or ex ternal compression and that the jugular veins are closer to the centr l venou region However only very experienced clinicians are good at detecting and interpreting the pulsations of the deep jugul r veins, while many medical st dents and house officers are uncertain in the examination of external jugular veins even when they are easily visible

At times the peripheral pressure ay be higher than the central due to an obstruction between the peripheral veins and the heart, but this may be recognized by a lack of fluctuation of the pressure with respiration, by variation of the pressure with changes in shoulder position or by the presence of an elevated pressure which does not rise further on abdominal compression as found in the hepato-jugular reflux of cardiac failure

On the other hand it is theoretically possible that the mean peripheral venous pressure might be lower than the central pressure if there are large A or V waves which are not transmitted peripherally because of venous valves. This is probably a very rare occurrence as the valves tend to be incompetent in such cases and pulse waves are often visible in the forearm veins, thus adding validity to peripheral pressure measurements.

There may be technical difficulties in measuring the venous pressure but they are usually easy to overcome at least in those cases in which a large vein is available for use.

Dr Selzer suggests that central venous pressure measurement may well take the place of the usual venous pressure test but, by contrast, central venous pressure procedures are fraught with complications that make them unsuitable for routine diagnostic use and they are often subject to error In some cases a catheter is advanced blindly and may pass retrograde into a peripheral vein or if it enters the right ventricle, it may cause dangerous ventricular ar rhythmias and give completely misleading pressures. Central venous catheterization cannot be repeated as easily as peripheral venipuncture and catheters left in place often become occluded or lead to infection.

Venous pressure measurements are particularly useful to confirm and reinforce impressions obtained from jugular veins and to convincingly determine for or against those somewhat uncommon and confusing entities, pericardial tamponade or constriction, and superior vena cava syndrome.

When cardiac failure is suspected from vague evidence a normal venous pressure and circulation time give strong evidence against a diagnosis which otherwise might be entertained longer than necessary

Theodore Lawrence, M.D
Chief Cardiovascular Section
Medical College of Pennsylvania Service
Veterans Administration Hospital
Philadelphia Pa. 19104

Reply

To the Editor

The disagreement between Dr Lawrence and myself is more philosophical than factual. We find no difficulty in training medical students and house officers in the proper interpretation of the jugular venous pulse Inasmuch as the same information can be obtained by a bloodless bedside examination, one can question the need of subjecting a patient to the pa nf l experience of puncturing a vein with a large bore needle. Bedside examination permits daily observ tions of changes in venous pressure, while daily manometric determ nations would hardly be practical Perhaps students and nterns m ght be induced to read the section on venous pressure and study the illustrations in *Diseases of the heart*, by Sir Thomas Lewis, published in 1933!

I am glad that Dr Lawrence brought up the question of the use of central venous pressure, because an obvious misunderstanding has arisen, which I hasten to correct My reference to central venous pressure was made as an argument that in seriously ill patients the present-day cardiologist has learned not to rely on peripheral readings of venous pressure but wants a measurement of right atrial pressure It was not my intention to imply that central venous pressure measurement may well take the place of the usual venous pressure test. The casual determination of central venous pressure is even more objectionable than a manometric reading of peripheral venous pressure, inasmuch as central venous pressure should be used *exclusively* in situations where the seriousness of the patient s condition requires *continuous monitori g* of right-sided pressures.

Arthur Selzer M.D
Director
Cardiopulmonary Laboratory
Presbyterian Hospital
San Francisco Calif

Book reviews

ADVANCES IN MICROCIRCULATION. Vol. 3. Edited by H. Harders, Hamburg. Basel, 1970, S. Karger AG, 114 pp. Price $14.00.

The third volume of *Advances in Microcirculation* is a good one, devoted to discussions of the influence of intravenously administered fat emulsions, thermography, microcirculation of peripheral nerves, the cochlea, histologous graphs of nucleus pulposus, and responses to smoking in man. Those studying the microcirculation will certainly find this to be an interesting book although the reviewer is impressed with the paucity of advances and work in this important field. Because of the need for more interest in the microcirculation physiologists should find this summary of important recent advances particularly useful to them. After all, it is the microcirculation which actually supplies the cells of the body with their circulatory needs.

UCLA FORUM IN MEDICAL SCIENCES. Vol. 13. CARDIOVASCULAR BETA-ADRENERGIC RESPONSES. Edited by Albert A. Kattus, Gordon Ross, and Victor Hall, Berkeley, 1970, University of California Press, 284 pp. Price $20.00.

The proceedings of a symposium held at the University of California School of Medicine in Los Angeles during February, 1968, are described in this publication. The beta-adrenergic responses were discussed primarily from the cardiovascular viewpoint. The participants reviewed the history of agents that stimulated or blocked the β-adrenergic responses as well as Dr. Ahlquist's original studies which introduced the concept of alpha- and beta-adrenergic sympathetic innovation. The actions of propranolol and catecholamines on the heart and blood vessels were discussed. The clinical applications of knowledge related to β-adrenergic responses contributed a fairly significant part of the symposium. As in all such symposia, the discussions are most interesting, for it is these which reflect the opinions of the participants and the shortcomings in knowledge. The uses of β-adrenergic blocking agents, particularly propranolol, are discussed a great deal. Practices concerning the use of propranolol up to 1968 are presented by the participants, all of whom studied this interesting drug. This is a good book on an extremely important subject.

GRANT'S CLINICAL ELECTROCARDIOGRAPHY: THE SPATIAL VECTOR APPROACH, ed. 2. Revised by Julian R. Beckwith, M.D. New York, 1970, A Blakiston Publication, McGraw-Hill Book Company, Inc., 225 pp. Price $9.95.

This second edition of Grant's approach to clinical electrocardiography brings these concepts up to date. Beckwith has not changed the presentations very much, however. Those who find this simplified approach to spatial vectorcardiography useful will want to own this new volume. This reviewer, however, finds such an approach to the clinical interpretation of electrocardiograms oversimplified. The detailed configuration and changes with disease of all the complexes of the ECG are extremely important in clinical diagnosis. The relatively crude mean values may be useful but they are not adequate for most effective practice of cardiology. Nevertheless, Grant's approach is satisfactorily presented in this volume for those interested in it.

THE CLINICAL RECOGNITION OF CONGENITAL HEART DISEASE. By Joseph K. Perloff, M.D. Philadelphia, 1970, W. B. Saunders Company, 608 pp. Price $25.00.

This book on the clinical recognition of congenital heart disease not only is of importance to the cardiologist but will also serve as an educational monograph. Perloff has written this monograph to assist doctors in becoming more efficient in diagnosis and management. His presentation is lucid and supported by many excellent illustrations and bibliographies. The physical examination and laboratory studies are emphasized. Perloff presents the simple bedside approach to diagnosis rather than reliance primarily on cardiac catheterization. It is extremely gratifying to see the doctor return to the bedside where the best medicine must eventually be practiced. The common heart defects are considered and clearly discussed. This is a very good book which should interest all pediatricians and internists as well as cardiologists.

CARDIOVASCULAR CLINICS. Albert N. Brest, M.D. Editor-in-chief. CONGENITAL HEART DISEASE, Daniel F. Downing, Guest Editor. Philadelphia, 1970, F. A. Davis Company, 330 pp. Price $10.00.

Brest edits another nice volume of cardiovascular clinics. The many contributors are well known in the field of congenital heart diseases. This volume includes the common congenital cardiac defects. It is written for the practicing physician and is an excellent up-to-date review of the subject which should not only interest pediatricians but all internists and cardiologists as well. The volumes in this series of cardiovascular clinics have been very good and this is no exception.

HEART AND VECTOR: PHYSICAL BASIS OF ELECTROCARDIOGRAPHY. Edited by H. C. Burger and H. W. Julius, Jr. The Netherlands, 1968, Philips Technical Library. Gordon and Breach, Publishers, Inc., 140 pp. Price $14.00.

Six of the 12 surviving embolized animals showed unequivocal electrocardiographic changes of myocardial infarction, four showed right or left bundle branch block and one showed T wave changes suggestive of ischemia. One dog showed no ECG changes following embolization but had a twofold increase in GOT a 14-fold increase in CPK and at autopsy a discrete healed infarction of the anterior wall of the left ventricle was present. Ten infarcted animal showed a twofold or greater increase in GOT and CPK. The range of serum GOT levels in the infarcted dogs was from 100 units per milliliter (200 per cent of normal) to 360 units per milliliter (700 per cent of normal) while the range of serum CPK was from 40 units (00 per cent of normal) to 80 units per milliliter (1400 per cent of normal) Two embolized animals showed no changes in either the GOT or CPK but had small areas of myocardial infarction on postmortem examination Fig 1 shows the serum enzyme levels for representative infarcted and control animals. There were no significant elevations in the GOT in the 12 control dogs, all of which survived the catheterization procedure In one control animal there was a fivefold increase in the CPK and in four others there was a twofold increase in the CPK. This finding is consistent with the recent observation of Michie and associates that the CPK is frequently elevated in patients following noncomplicated cardiac catheterization particularly when selective coronary arteriography is performed

The hearts from 11 of 12 surviving embolized animal showed multiple discrete healed subendocardial infarctions. One heart exhibited no gross lesions but did contain visible microspheres on the epicardial surface and mild fibrosis and cytolysis were present on microscopic examination. This dog had no ECG changes after embolization but had significant enzyme elevations

Using the combination of techniques employed in other laboratories, we have developed a model yielding reproducible myocardial infarction The standardized doses of microspheres delivered by selective coronary artery catheterization produced characteristic changes in the ECG and rises in the serum enzymes in the majority of animals embolized. The resultant myocardial lesions were consistent in their magnitude, distribution, and morphology This degree of consistency is not encountered in other studies where the dose of microspheres is not standardized for estimated heart weight[1] or selective coronary catheterization was not used for their injection. When this technique was used there were no deaths after the immediate operative period. The absence of late deaths makes this model useful for serial and long term studies, particularly since the chest has not been opened, the heart and vessels have not been manipulated and the cardiac nerve supply is intact

J D Palmer M.D Ph.D
R I O'Rourke M.D
M S. Olsen Ph.D
R A Pinckard, Ph.D
University of Arizona
College of Medicine
Tucson Ariz.

REFERENCES

1 Agress, C. M Rosenberg M J Jacobs, H I et al. Protracted shock in the closed chest dog following coronary embolization with graded microspheres, Amer J Physiol 1 0:336, 1952.

2. Jacobey J A Taylor W J Smith, G. T et al. A new therapeutic approach to acute coronary occlusion, Amer J Cardiol 9:60, 1962.

3 Guzman S V Swenson, E. and Mitchell R. Mechanism of cardiogenic shock, Circulation Res. 10:746, 1962.

4 Bloch J H Pierce, C H Manax, W G., et al. Treatment of experimental cardiogenic shock, Surgery 58:197 1965

5 Bergmeyer H U Methods of enzymatic analysis New York, 1965 Academic Press, Inc. pp. 837-859

6. Michie D D Conely M L, Carretta, R. F et al Serum enzyme changes following cardiac catheterizations with and without selective coronary arteriography Amer J Med. Sci. 200:11 1970.

Books received

Aktuelle Probleme in der Angiologie—Thrombolyse bei Obliterierender Arteriopathie, Band 8. By M. Martin, W. Schoop, and E. Zeitler. Wien, Germany 1970, Verlag Hans Huber. 155 pages.

Annals of the New York Academy of Sciences, Vol. 170, Art. 2, pages 407-836, International Conference on Bioelectrical Impedance. Edited by Simon E. Markovich, New York, 1970. New York Academy of Sciences, 429 pages. Price $26.50.

Body Fluid Replacement in the Surgical Patient. By Charles L. Fox and Gabriel G. Nahas, New York, 1970, Grune & Stratton, Inc., 374 pages. Price $15.00.

Interferon—Proceedings of a Symposium Sponsored by the New York Heart Association. Boston, 1970, Little Brown & Co., 268 pages. Price $8.50.

The International Handbook of Medical Science. Edited by David Horrobin and Alexander Gunn, New York, 1970, G. P. Putnam & Sons, 744 pages. Price $16.00.

Klinische Pathophysiologie der Atmung. By A. A. Bühlmann and P. H. Rossier. New York, 1970, Springer Verlag, 219 pages. Price $18.70.

Learning Mechanisms in Smoking. By William A. Hunt, Chicago, 1970, Aldine Publishing Co. 237 pages. Price $8.95.

Modern Trends in Biomechanics, I. Edited by David C. Simpson, New York, 1970, Appleton-Century-Crofts, 273 pages. Price $16.00.

Overcoming the Fear of Death. By David Cole Gordon, New York, 1970, The Macmillan Co., 115 pages. Price $3.95.

The Pharmacological Basis of Therapeutics, ed. 4. By Louis S. Goodman and Alfred Gilman, New York, 1970, The Macmillan Co., 1794 pages. Price $25.00.

Running for Your Life. By Bill Emmerton, as told to Oscar H. Schested, New York, 1970, World Publishing Co., 118 pages. Price $5.95.

Julius has condensed in a small book the important contributions made by Prof Herman C. Burger to electrocardiography and vectorcardiography Professor Burger's work has been outstanding and fully appreciated the world over and this tribute to him and his work is an excellent idea. Julius renders a fine service in bringing together these important studies of Burger The book includes chapters on instruments, placement of electrodes, Einthoven's triangle, the electric dipole heart and lead vectors, polar vectors, ventricular gradient, multipolar effects, clinical applications, and other aspects of theoretic electrocardiography The book is actually a dedication to H C Burger This nice book should interest all concerned with electrocardiography Prof Burger's bibliography in this field is also included for those who wish to study the original publications

THE MANAGEMENT OF GERIATRIC CARDIOVASCULAR DISEASE. By Raymond Harris M D Philadelphia, 1970 J B Lippincott Company 306 pp. Price $16.50.

Harris has written an interesting, though relatively small book on an important subject. Physicians fail too often to realize that diseases in older patients require considerations in management which differ markedly from those for younger people. As this book indicates, old people almost always have several diseases simultaneously most of them degenerative Furthermore, old people are frequently more sensitive to drugs than are young people. They respond slowly to questioning, and they must be handled more cautiously during physical examination. Their cardiovascular disease usually involves arteriosclerosis, hypertension, or chronic pulmonary disease with cor pulmonale, and often all three together Harris discusses these in the usual fashion. He included chapters on congestive heart failure, arrhythmias, occlusive arterial disease and pre- and postoperative care of the aged cardiac patient. This book emphasizes the importance of geriatric cardiology in clinical medicine The bibliography is complete and the index is good.

RECENT ADVANCES IN BLOOD COAGULATION Edited by L. Poller M D M R.C.S (Eng) M D Path. London, 1969 J & A. Churchill Ltd 362 pages. Price $18 00.

This book, edited by Dr Poller is concerned with one of the most important problems in clinical medicine There are patients whose blood will not clot normally when it should and there are those whose blood will clot when it should not. The same physician is often confronted with both during his practice. To understand and manage these patients adequately he should know the general principles of blood coagulation. With the assistance of many outstanding contributors Poller has gathered a series of papers dealing with the important aspects of blood clotting There are 16 chapters in the book which are concerned with a wide range of aspects of blood coagulation, varying from mechanisms and biochemistry platelet adhesion and aggregation to clinical applications. The style is clear and the reviews of the selected aspects of coagulation are thorough though concise. The contributors have maintained a practical point of view while integrating new and complex aspects of blood coagulation with already established ones. This is a good source of fundamental and practical information which should interest all doctors. This book is a good contribution to the medical literature and worth careful study

COMPUTERS IN ELECTROCARDIOGRAPHY By Josef Wartak, M D B.Sc. Springfield Ill 19 0, Charles C Thomas, Publisher 250 pages. Price $19.50.

This is a highly specialized subject which should interest those planning or already concerned with the use of computers in the analysis of electrocardiographic recordings. The average physician may wish to review this book to learn more about this type of ECG analysis and interpretation. The author briefly discusses the principles of electrocardiography and computers. Chapters are devoted to acquisitions and processing of electrocardiograms, and various systems employed for ECG processing and analysis. The presentations are good Anyone engaged in this field of electrocardiography will find this book interesting and should want to own a copy regardless of his ideas and systems of computer applications in electrocardiography

Books received

Aktuelle Probleme in der Angiologie—Thrombolyse bei Diabetischer Arteriopathie, Band 8. By M. Martin, W. Schoop, and E. Zeitler Wien, Germany 1970, Verlag Hans Huber 155 pages.

Annals of the New York Academy of Sciences, Vol. 170, Art. 2, pages 407-836, International Conference on Bioelectrical Impedance. Edited by Simon E. Markovich, New York, 19 0, New York Academy of Sciences, 429 pages. Price $26.50.

Body Fluid Replacement in the Surgical Patient By Charles L. Fox and Gabriel G. Nahas, New York, 1970, Grune & Stratton, Inc., 374 pages. Price $25.00.

Interferon—Proceedings of Symposium Sponsored by the New York Heart Association. Boston, 1970, Little, Brown & Co., 268 pages. Price $8.50.

The International Handbook of Medical Science. Edited by David Horrobin and Alexander Gunn, New York, 1970, G. P. Putnam & Sons, 744 pages. Price $16.00.

Klinische Pathophysiologie der Atmung. By A. A. Bühlmann and P. H. Rossier New York, 1970, Springer Verlag, 219 pages. Price $18.70.

Learning Mechanisms in Smoking. By William A. Hunt, Chicago, 1970, Aldine Publishing Co 237 pages. Price $8.95

Modern Trends in Biomechanics, 1 Edited by David C. Simpson, New York, 1970, Appleton-Century-Crofts, 273 pages. Price $16.00.

Overcoming the Fear of Death. By David Cole Gordon, New York, 1970, The Macmillan Co., 115 pages. Price $3.95.

The Pharmacological Basis of Therapeutics, ed. 4. By Louis S. Goodman and Alfred Gilman, New York, 1970, The Macmillan Co., 1 794 pages. Price $25.00.

Running to Your Life. By Bill Emmerton, as told to Orv H. Sebested, New York, 1970, World Publishing Co., 118 pages. Price $5.95

Announcements

POSTGRADUATE SYMPOSIUM ON STREPTOCOCCAL DISEASE RECOGNITION UNDERSTANDING, AND MANAGEMENT sponsored by the University of Minnesota Medical School Department of Laboratory Medicine in conjunction with the National Institute of Allergy and Infectious Diseases of the National Institutes of Health and the Eli Lilly Company will be held May 12 to 14 1971 in the Mayo Auditorium at the University of Minnesota Health Sciences Center Minneapolis, Minn. An outstanding national and international faculty has been recruited for this 3 day course which is approved for 18 hours AAGP credit. The fee is $90 00. For information write Dr John M Matsen or Dr Lewis W Wannamaker University of Minnesota Hospitals, Minneapolis, Minn. 55455

THE FONDATION DE PHYSIOPATHOLOGIE PROFESSEUR LUCIEN DAUTREBANDE will award during the year 1973 an international prize of about 500,000 Belgian francs ($10,000) It will be a reward for work on human or animal physiopathology such work preferably having therapeutic implications. For further information about this prize please write to the office of the Foundation 35 Chaussée de Liège 5200 HUY Belgium.

American Heart Journal

June 1971 Volume 81 Number 6

Editorial

Lumbar sympathectomy for chronic occlusive arterial disease

R. L. Richards
Glasgow Scotland

In the days before direct arterial surgery was widely practiced (that is, prior to 1950) sympathectomy was the main surgical procedure which was done to improve the circulation in the extremities in cases of chronic occlusive peripheral arterial disease. The rationale of the operation was the belief that in most cases, in addition to the organic changes in the arteries of the limb some degree of vasospasm was also present and that this could be relieved by sympathectomy This clinical concept was never based on good evidence. Interruption of the sympathetic pathways to a limb will abolish normal vasoconstrictor tone and as a result there is peripheral vasodilatation The vessels mainly affected are the arterioles and arteriovenous anastomoses in the skin of the foot. The increase in blood flow is maximal within 48 hours of the operation and then declines steadily after two weeks the blood flow in a sympathectomized extremity is only about double the preoperative flow The digits, however may remain warm for several months.

When a patient has occlusive disease of the main arteries of the lower limb he usually presents with intermittent claudication. The precise mechanism of claudication is still uncertain but it is accepted that this symptom is due to an inadequate blood supply to the muscles during exercise. Although there is some evidence that there are sympathetic vasoconstrictor nerves to skeletal muscle, and that these do exert some degree of vasoconstrictor tone there is no evidence that these fibers play any part in providing the increased blood flow in response to exercise. On physiological grounds, therefore, there is no reason to think that sympathectomy will help the patient with intermittent claudication Nonetheless, there are those who still maintain that interruption of the sympathetic supply whether by operation or by injection of phenol or alcohol is of value in these circumstances.[1-4] From the clinical aspect it is extremely difficult to show that sympathectomy improves intermittent claudication Studies on the natural history of claudication all show that spontaneous improvement occurs in most patients. In all the good clinical trials of drugs for claudication the one consistent finding has been the improvement which has been observed in patients who are taking placebo tablets. When critical studies have been made on the effect of sympathectomy it has been noted that in those patients who say that their claudication is improved it is

From the Western Infirmary Glasgow W.1, Scotland.

Vol. 81, No. 6 pp. 735-737 June 1971

uncommon to find any objective evidence to support their opinion [4,5] It must be concluded therefore that lumbar sympathectomy seldom relieves intermittent claudication and that in these patients who claim benefit other factors such as the natural tendency to spontaneous improvement slower walking loss of weight cessation of smoking and in some cases improvement of their cardiac status are more likely to be responsible

Even if sympathectomy does not help the patient whose only complaint is of intermittent claudication some advocates for the operation claim that it should nevertheless be done in such cases to improve the circulation to the skin of the extremity—that is that sympathectomy has a prophylactic value in preventing the future development of ischemia of the foot This concept is one which has not been critically evaluated A sympathectomized foot undoubtedly remains warmer and has an increased total blood flow at rest even years after the operation It is not affected to the same extent by the vasoconstriction of cold and certain other agents which act through sympathetic pathways and it is entirely possible that this might have a protective value The incidence of severe ischemia leading to amputation in patients who present with intermittent claudication is surprisingly low—about 8 per cent over a period of 5 to 10 years [6,7] It would therefore require a large number of patients divided into sympathectomized and nonsympathectomized groups and followed over many years to obtain a clear-cut answer to this question

Nowadays however lumbar sympathectomy is usually done mainly for the patient who has ischemic symptoms in the foot either definite nutritional changes, or pain or both and who is considered unsuitable either as a result of arteriography or because of his general condition for direct arterial surgery It is generally believed that in such cases the operation will increase skin blood flow in the foot and thus improve nutrition promote healing and relieve rest pain A survey of recent papers on this subject indicates that 55 to 60 per cent of patients who have a sympathectomy for these reasons are considered improved.[8] These are clinical impressions, however and are entirely uncontrolled. There is much need for a study in which patients who have chronic ischemia of the foot due to obliterative arterial disease are unsuitable for direct arterial surgery and are not in severe pain are randomly allocated to two groups—of which one has sympathectomy either by operation or by a phenol or alcohol block and the other is treated conservatively It is recognized that occasionally in cases of this type lumbar sympathectomy may be followed by a rapid deterioration in the condition of the sympathectomized limb the so-called paradoxical reaction It is thought that this is due either to the effect of postoperative hypotension or to damage to an atheromatous aorta by retractors especially when the operation is done on the left side, and the dislodgement of portions of thrombus or atheroma which are carried distally and occlude previously patent arteries in the limb [9] It is therefore not surprising that the value of lumbar sympathectomy even for patients with ischemic manifestations in the foot should also be questioned [10] At best it is a valuable procedure in patients whose marginally adequate circulation becomes dangerously reduced by normal vasoconstrictive mechanisms [11]

In summary therefore lumbar sympathectomy does not relieve intermittent claudication and it is questionable whether it has any prophylactic value in a patient who still has an adequate blood supply to the foot. Clinical impressions suggest that when the operation is done to relieve ischemic manifestations in the foot it is successful in more than half the cases but a critical assessment of these results has still to be made and there is a small risk that the operation may be followed by a worsening of the situation

REFERENCES

1 Barcroft, H and Swan, H J C. Sympathetic control of human blood vessels, London, 1953 Edward Arnold & Co.
2. Smithwick R. H Lumbar sympathectomy I the treatment of obliterative vascular disease of the lower extremities, Surgery 12 115, 567 1957
3 Mackenzie D C. and Lowenthal, J Lumbar sympathectomy and claudication distance, Surg Gynec. Obstet. 114:503 1962.

4. Strandness, D. E., and Bell, J. W.: Critical evaluation of the results of lumbar sympathectomy, Ann. Surg. 160:1021, 1964.
5. Myers, K. A., and Irvine, W. T.: An objective study of lumbar sympathectomy. I. Intermittent claudication, Brit. Med. J. 1:879, 1966.
6. Bloor, K.: Natural history of arteriosclerosis of the lower extremities, Ann. Roy. Coll. Surg. Eng. 28:36, 1961.
7. Begg, T. B., and Richards, R. L.: The prognosis of intermittent claudication, Scot. Med. J. 7:341, 1962.
8. Richards, R. L.: Peripheral arterial disease, Edinburgh, 1970, E. & S. Livingstone, Ltd.
9. Bergan, J. J., and Trippel, O. H.: Arteriograms in ischemic limbs worsened after lumbar sympathectomy, Arch. Surg. 85:643, 1962.
10. Tice, D. A., Reed, G. E., Mesulam, E. J., Clemente, E., and Redisch, W.: Lumbar sympathectomy. Effect on vascular responses in the lower extremity of patients with arteriosclerosis obliterans, Arch. Surg. 87:461, 1963.
11. Shaw, R. S., Austen, W. G., and Stipa, S.: A ten year study of the effect of lumbar sympathectomy on the peripheral circulation of patients with arteriosclerotic occlusive disease, Surg. Gynec. Obstet. 119:486, 1964.

Clinical communication

Emergency management of pacemaker failure by means of radio-frequency energy

Riccardo Benvenuto, M.D., F.I.C.S.
Peter Mayer, M.D.
Chicago, Ill.

Radio-frequency energy transmitted through the intact skin has been used by us for the past several years to temporarily stimulate a previously implanted pacemaker with depleted batteries. This is achieved by simply applying a radio-frequency antenna on the skin over the implanted pacemaker. It is therefore possible by means of a simple external maneuver to convert an emergency replacement for battery failure into an elective case without crisis.

The high-energy radio-frequency transmitter is produced by the Medtronic Company under the name of External Rate Control Model 5855 (Fig. 1). The device consists of an AC powered* high energy radio frequency transmitter with a coil antenna encased in rubber. This antenna is placed on the skin over the implanted pacemaker. Bursts of radiofrequency energy are produced by the unit and transmitted through the antenna to the pacemaker where existing circuitry acts as the receiver. As the name implies, the rate controller was originally devised and produced by the manufacturer as a means of temporarily increasing the rate of an implanted pacemaker and to test the integrity of an implanted demand pacemaker system.[1] We found that the radio frequency transmitter is capable of a much more important function. We use it to increase the output of standard pacemakers with depleted batteries (therefore no longer capable of pacing) to again deliver to the heart an amount of electrical current sufficient to restart effective pacing. All this is accomplished through the intact skin.

We have been unable to find previous reports in the medical literature indicating this use; therefore we believe this is an original observation.

Material and methods

In our patients with heart block or other brady- and tachyarrhythmias requiring pacing, we use the pulse generators of different types produced by the Medtronic Company. In recent years, the type most frequently used is the so-called demand or ventricular inhibited pacemaker. The usual mode of battery failure or battery depletion observed with these pulse generators is a sudden cessation of effective stimulation of the heart. As observed on the electrocardiogram, the phenomenon is characterized by the presence of pacemaker artifacts of small amplitude occurring at irregular intervals (if the sensing circuit is normal) and not followed by the QRS complex (Fig. 2). It has been our experience

From the Department of Surgery and Medicine, Grant Hospital, Chicago, Ill.
Received for publication May 18, 1970.
*A battery-operated unit has been supplied to us by the Medtronic Company on a special order basis.

Fig. 1 The radio-frequency transmitter with the coil antenna.

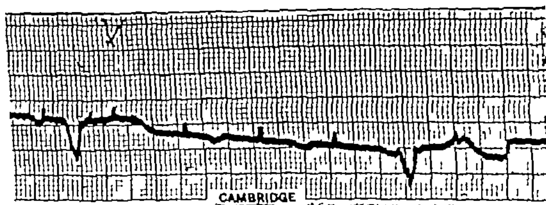


Fig. 2 Lead I of patient G. F (hospital No. 4046931) showing pacemaker failure.

that this situation can be instantaneously corrected by simply applying the antenna of the radio-frequency transmitter on the skin over the failing pacemaker When this is done the amplitude of the pacemaker impulse is increased and effective pacing will resume (Fig 3)

We have been using this *technique in* all our emergency battery failures and have constantly observed the above results. To date, six patients have been treated in this way and in all an elective generator change was performed after maintaining the patient's heart rate at adequate levels by

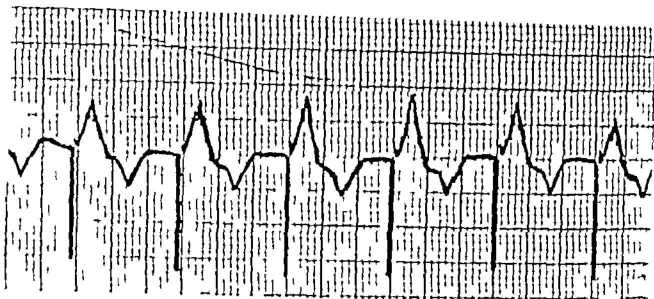


Fig 3 Lead I of same patient as in Fig 1 obtained after application of the radio-frequency antenna.

using the radio-frequency transmitter In no instance have we had to resort to the standard techniques of rapidly exteriorizing the pacemaker and connecting the electrodes to an external pulse generator or of inserting a new temporary electrode catheter for interim pacing as described in the literature[3]

Experimental work

In order to confirm our clinical observations that an implanted pacemaker with depleted batteries can be activated externally by means of radio-frequency energy the following experiment was carried out A Medtronic demand pacemaker (Model 5841) with depleted batteries was connected across a 500 ohm load to a standard electrocardiograph machine An artifact of 16 mm of amplitude* was observed (Fig 4) When the antenna of the radio-frequency transmitter was placed over the pacemaker the amplitude of the pacemaker impulse increased to 24 mm * (Fig 5) The phenomenon could be reproduced at will indefinitely by applying and removing the antenna

*The pacemaker impulse is here quantitated in millimeters instead of the familiar millivolts because direct [illegible] amplitude th calibration 1 mm = 1 m[illegible]ed in human electrocardiogram is not possible in this particular situation. It must be noted however that here we are dealing with one single tracing; therefore, the relative values of the pacemaker impulses—with and without the radio-frequency boost—are meaningful and directly comparable.

Discussion and conclusions

One current procedure for emergency pulse generator replacement in case of battery failure consists of an emergency exteriorization of the pacemaker under local anesthesia with connection of the electrodes to an external pulse generator Others[4] prefer the transvenous implantation of a second electrode catheter connected to an external pacemaker Both these techniques have undesirable features. This is usually an emergency situation with the patient in a low cardiac output state frequently leading to cerebral hypoxia and convulsions. Death may occur The generator change must be carried out without delay and rapidly as possible yet both the standard techniques now in use are time consuming In addition each one of them has specific undesirable features. The emergency surgical exteriorization of the depleted pacemaker is usually carried out in environments—such as the hospital emergency room—providing less than optimum conditions of lighting surgical instrumentation and observance of sterile techniques. Infection may result a much dreaded complication in a situation where large foreign bodies (the pacemaker and the electrodes) are present When it is elected to implant a temporary transvenous electrode the patient is exposed to all the complications of this additional procedure and to the difficulties possibly deriving from competitive pacing All this can be avoided

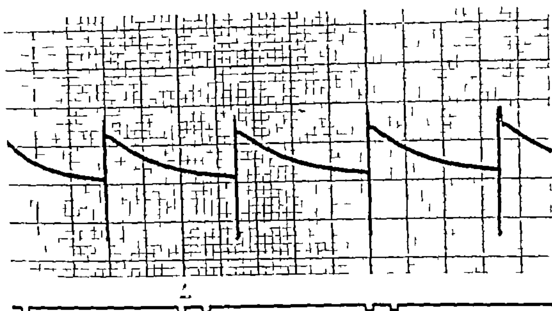


Fig. 4 Tracing obtained from removed failing pacemaker (see text for explanation.)

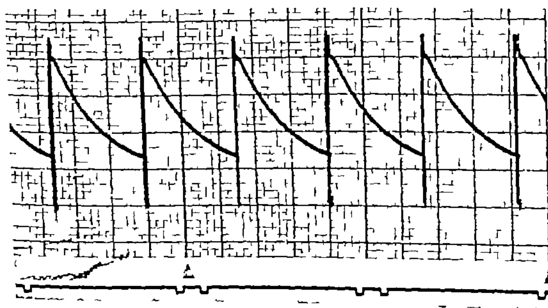


Fig. 5 Tracing obtained from same pacemaker as in Fig. 4 after application of the radio-frequency antenna.

with the technique here described which is totally external and instantaneous. The radio-frequency stimulation will reach the depleted pulse generator through the intact skin and effective pacing will resume. The patient can thus be paced at an adequate rate until the operating room is ready for a definitive pacemaker change as in an elective case. An emergency situation is therefore changed into an elective procedure without crisis. We have paced patients in this manner for as long as thirteen hours. Longer periods may be possible. In the future this safety measure may be made available to the patients and their families for emergency use in case of sud

den pacemaker failure outside the hospital.

The possibility of using the external rate control to augment failing pacemakers of different manufacture should be considered. Ability of the rate control to increase the rate in any model would suggest a trial to determine if the output might also be augmented. Remotely, the application of radiofrequency energy at identical rates to pacemakers not responding to rate change might be tried for increasing output temporarily.

Because of the ability of the external rate control to increase output of failing pacemakers, caution must be used in assessing pacemaker function in the usual manner. If a ventricular inhibited pacemaker (shut off by the patient's adequate rhythm) has its rate increased by application of the rate control in an attempt to demonstrate pacemaker integrity, poor pacemaker output may be masked by the additional energy supplied by the rate control. This may result in normal pacemaker capture even though the tested pacemaker is failing.

Summary

Pacemaker failure due to premature battery depletion is usually an emergency situation requiring immediate correction. Current techniques used to cope with this problem require either a rapid surgical exteriorization of the failing pulse generator with connection to an external pacemaker or the insertion of a second temporary pacemaker catheter for interim pacing. Both techniques are time consuming and have other undesirable features. Radiofrequency energy stimulation of the failing pacemaker has been used routinely by us to solve this problem. The failing pacemaker is activated through the intact skin by means of a radio frequency antenna placed on the skin over the pacemaker. Existing circuitry in the pacemaker functions as the receiver. Pacing will resume and an emergency situation will thus be converted into an elective pacemaker replacement.

REFERENCES

1. Technical information: External rate control, Medtronic, Inc., Minneapolis, Minn. May 1968.
2. Sowton, E., and Barr, I.: Emergency management of patients with missed pacing, Amer. Heart J. 79:458, 1970.

T wave abnormalities in the electrocardiograms of top-ranking athletes without demonstrable organic heart disease

Nora Hanne-Paparo, M.D.
Martin H. Wendkos, M.D.
Daniel Brunner, M.D.
Tel Aviv, Israel

Many studies already have shown that a program of intensive physical training characteristically elevates the level of vagal control upon the cardiac apparatus.[1-4] Consequently, it was anticipated that an electrocardiographic survey (which was conducted at the Wingate Institute in 1967 by one of us, N. H.) of young top-ranking Israeli athletes would disclose, in the routine resting conventional 12 lead electrocardiogram (ECG) of this sample of the population, little more than a high incidence of abnormal pacemaker activity or disturbed sino-auricular or atrioventricular conduction. However, in this sample (of which all subjects are continuing to function as members of national teams) it was unexpectedly discovered that, in addition to the relative frequency of such findings, there were 7 other instances of a "repolarization disorder" as well, despite the absence of any clinical evidence of structural heart disease. The "repolarization disorder" was accompanied regularly by a minimal sinus bradycardia without associated conduction disturbances and the changes of the T wave, which were its hallmark, consisted of distinct inversions of this deflection either in multiple limb leads alone (2 cases) or in both multiple limb and precordial leads (5 cases). Moreover, in 4 instances it was noted that the T waves were normalized immediately after the completion of a standardized non-exhausting amount of measured exercise. In the other 3, the same exercise test did not modify the T waves to any material degree. Further elaboration of the ECG data and a brief discussion of some of the possible implications comprise the remainder of this report.

The ECG data

The pertinent findings in the 7 athletes are summarized in Table I and, in addition, two representative ECG's taken while the subjects rested are depicted in Figs. 1 and 2. These ECG's typify the changes in the tracings of 5 members of this group of athletes and, as is evident, the essential abnormalities were confined to the T waves in multiple limb and precordial leads. The ECG's of the other 2 athletes, taken while at rest, were different, inasmuch as T wave changes of the same order were confined to Leads II, III, and aV_F only. It was noted also that when the T wave inversions were present in the

From the Donolo Institute of Physiological Hygiene, Tel Aviv University, Tel Aviv, Israel.
Received for publication May 29, 1970.
*Visiting Consultant; Member of the Faculty, Jefferson Medical College, Philadelphia, Pa.

Table I

Athlete	Age	Resting blood pressure (mm Hg)	T inversions (rest)	Immediately after exercise (T wave)	3 minutes after exercise (T wave)
J H	20	135/60	L and I	Normal	Inverted
Z \	17	150 85	L	Normal	Normal
C S	20	120/80	L and I	Inverted	Inverted
D S	27	120/75	I and I	Normal	Inverted
T G	29	125/80	L and I	Inverted	Inverted
D G	23	120/75	L	Normal	Inverted
M L	23	105/ 0	L and I	Inverted	Inverted

Abbreviations L, multiple limb leads P multiple precordial leads.

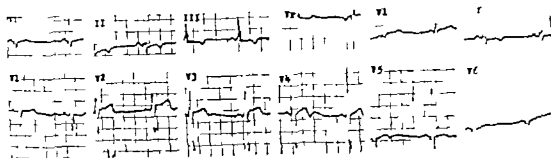
precordial leads they were always absent in the leads made with the exploring electrode placed close to the sternum Because of this feature the abnormalities we encountered cannot be attributed to a persistent juvenile T wave pattern as defined by various authors who have described its essential characteristics.[8,12] More likely because of the *localization of the T wave* distortions we believe they should be perceived as an expression of a true but benign repolarization disorder involving predominantly the left ventricular myocardium

For obvious reasons we sought to determine the influence of increased cardiac work upon the T wave abnormalities which have been described For this purpose we employed a standardized exercise test (150 watts of work performed for 3 minutes) and the results indicated that two types of ECG responses occurred following this maneuver In 4 members of this sample this amount of exercise abolished the T wave abnormalities (Table I Fig 1) and in the 3 remaining athletes it did not (Table I Fig 2) Moreover with one exception normalization of the T waves in the former group was a brief event and within 3 minutes after the completion of the test the abnormalities of the T wave had returned (Table I Fig 1) Perhaps the normalization for more than 3 minutes in the one instance (Table I) can be related to the circumstance that the particular athlete in whom this phenomenon was observed was the only one younger than 18 years of age and the only one who displayed fairly marked evidence of vasomotor lability as evidenced by large swings of the systolic blood pressure and heart rate following exercise It is also of interest that normal T waves were observed in a subsequent routine resting ECG of this same athlete after he had interrupted his program of physical training for several *months and had refrained from any par*ticipation in competitive sports activity during this same period

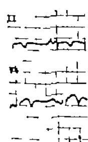
Discussion

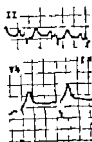
So far as we have been able to determine similar abnormalities have been described in the ECG s of only two top-ranking American athletes during the past decade The first was the case of a young professional athlete who was studied intensively by Likoff Segal and Dreifus.[13] He was 24 years of age and was nationally re*nowned for his athletic achievements.* He never displayed any symptoms suggestive of cardiac impairment and a variety of examinations including coronary arteriography failed to confirm the presence of any structural cardiopathy These studies were undertaken merely because of the chance discovery of puzzling T wave inversions in multiple leads of a routine resting ECG Regrettably the protocol did not contain specific information pertaining to the nature of the ECG response to measured exercise but in all likelihood the above case can be considered to be a counterpart of those which constitute the basis of our report.

The second case came to our attention



D.J. 27 yrs





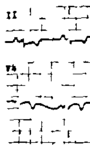
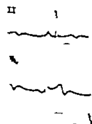
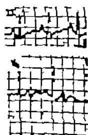


Fig 1 ECG of an outstanding football player and member of the Israeli national team. Note the sinus bradycardia associated with inverted T es in limb and precordial leads, at rest, nd the normalization of the T ves immediately after standardized exercise test



G.B. 20 yrs





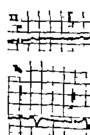


Fig. 2. ECG' of an outstanding football player Note inverted T s in multiple limb and precordial leads, at rest as ell as after exercise.

Table I

Athlete	Age	Resting blood pressure (mm Hg)	T inversions (rest)	Immediately after exercise (T wave)	3 minutes after exercise (T wave)
J H	0	135/60	L and P	Normal	Inverted
Z V	17	150/85	L	Normal	Normal
G S	20	1[illegible]0/80	L and P	Inverted	Inverted
D S	27	1[illegible]0/75	L and P	Normal	Inverted
T G	[illegible]9	125/80	L and P	Inverted	Inverted
D G	23	1[illegible]0/75	L	Normal	Inverted
M L	23	105/70	L and P	Inverted	Inverted

Abbreviations L, multiple limb leads P multiple precordial leads.

precordial leads they were always absent in the leads made with the exploring electrode placed close to the sternum Because of this feature the abnormalities we encountered cannot be attributed to a persistent juvenile T wave pattern as defined by various authors who have described its essential characteristics[9, 11] More likely because of the localization of the T wave distortions we believe they should be perceived as an expression of a true but benign repolarization disorder involving predominantly the left ventricular myocardium

For obvious reasons we sought to determine the influence of increased cardiac work upon the T wave abnormalities which have been described For this purpose we employed a standardized exercise test (150 watts of work performed for 3 minutes) and the results indicated that two types of ECG responses occurred following this maneuver In 4 members of this sample this amount of exercise abolished the T wave abnormalities (Table I Fig 1) and in the 3 remaining athletes it did not (Table I Fig 2) Moreover with one exception normalization of the T waves in the former group was a brief event and within 3 minutes after the completion of the test the abnormalities of the T wave had returned (Table I Fig 1) Perhaps the normalization for more than 3 minutes in the one instance (Table I) can be related to the circumstance that the particular athlete in whom this phenomenon was observed was the only one younger than 18 years of age and the only one who displayed fairly marked evidence of vasomotor lability as evidenced by large swings of the systolic blood pressure and heart rate following exercise It is also of interest that normal T waves were observed in a subsequent routine resting ECG of this same athlete after he had interrupted his program of physical training for several months and had refrained from any participation in competitive sports activity during this same period

Discussion

So far as we have been able to determine, similar abnormalities have been described in the ECG s of only two top-ranking American athletes during the past decade. The first was the case of a young professional athlete who was studied intensively by Likoff Segal and Dreifus.[13] He was 24 years of age and was nationally renowned for his athletic achievements. He never displayed any symptoms suggestive of cardiac impairment and a variety of examinations including coronary arteriography failed to confirm the presence of any structural cardiopathy These studies were undertaken merely because of the chance discovery of puzzling T wave inversions in multiple leads of a routine resting ECG Regrettably the protocol did not contain specific information pertaining to the nature of the ECG response to measured exercise but in all likelihood the above case can be considered to be a counterpart of those which constitute the basis of our report.

The second case came to our attention

genic component among the causes for the distorted T waves but, in our view such a neurogenic factor would more likely be related to a state of "vagotonia" rather than to one of sympathicotonia. Conceivably a concomitant redistribution of the potassium ion within the myocardial cell in conjunction with a physical conditioning program could under certain circumstances also contribute to the development of such T wave changes, without interfering with myocardial contractility and maximum cardiac performance but of course we must await more experimental evidence in order to substantiate such a thesis. In the meantime we shall make additional observations which hopefully may clarify the meaning of this feature of the athletic heart syndrome.

Conclusions

1 Major T wave abnormalities were observed in the routine conventional 12 lead resting ECG's of 7 young top-ranking athletes in Israel even though none exhibited any clinical evidence of a congenital or acquired form of heart disease.

2. Over a period of three years since the discovery of the ECG abnormalities, these athletes have continued to participate regularly in their chosen sport and consistently have been able to maintain a record of outstanding performance in competitive games.

3 In four instances, a standardized exercise test abolished the T wave abnormalities but with one exception the normalization of the T waves resulting from this maneuver did not persist for longer than 2 minutes.

4. It has been suggested that in the 3 remaining cases, a more strenuous exercise test than the one we customarily employed might have been followed by a reversal of the T waves.

5 The meaning of the ECG abnormalities in this group of athletes is still not completely understood but it is suspected that they represent a benign ECG phenomenon due to increased vagal tone in conjunction with shifts in myocardial potassium content.

REFERENCES

1. White, P. D.: Heart disease, ed. 3, New York, 1949, The Macmillan Company.
2. Beckner, G. L., and Winsor, T.: Cardiovascular adaptation to prolonged physical effort, Circulation 9:835, 1954.
3. Beswick, F. W., and Jordan, R. C.: Cardiological observations at the Sixth British Empire & Commonwealth Games, Brit. Heart J. 23:113, 1961.
4. Smith, W. G., Cullen, K. J., and Thornburn, I. O.: Electrocardiograms of marathon runners in 1962 Commonwealth Games, Brit. Heart J. 26:469, 1964.
5. Dennison, A. D.: Athletics and the heart, J. Indiana Med. Ass. 57:850, 1964.
6. Hammer, W. M.: Physiological and performance changes during periods of football training and re-training, J. Sports Med. 5:72, 1965.
7. James, T. N., Frogatt, P., and Marshall, T. K.: Sudden death in young athletes, Ann. Intern. Med. 67:1013, 1967.
8. Gott, P. H., Roselle, H. A., and Crampton, R. S.: The athletic heart syndrome—5-year cardiac evaluation of a champion athlete, Arch. Intern. Med. 122:340, 1968.
9. Littman, D.: Persistence of the juvenile pattern in the precordial leads of healthy adult negroes, AMER. HEART J. 32:370, 1946.
10. Wasserburger, R. H.: Observations on the juvenile pattern of adult negro males, Amer. J. Med. 18:428, 1955.
11. Grusin, H.: Peculiarities of the African's electrocardiogram and the changes observed in serial studies, Circulation 9:860, 1954.
12. Somers, K., and Rankin, A. M.: Electrocardiogram in healthy east African men, Brit. Heart J. 24:542, 1962.
13. Likoff, W., Segal, B., and Dreifus, L.: Myocardial infarction patterns in young subjects with normal coronary arteriograms, Circulation 26:373, 1962.
14. Lorber, S.: Personal communication.
15. Venerando, A., and Rulli, V.: Frequency morphology and meaning of the electrocardiographic anomalies found in olympic marathon runners and walkers, J. Sports Med. 4:135, 1964.
16. Dembo, A. G.: Chronic heart strain in sportsmen, *in* Karpman, V. L., and Kukolevsky, G. M., editors: Heart and sport, Moscow, 1968, p. 427.

through a personal communication from a physician who had made an ECG survey of a team of professional American basketball players repeatedly rated as national champions in the United States.[14] The individual in question is one who has annually gained a reputation as the star of the team and all accounts of his athletic prowess even up to the present time have indicated that he has been able to maintain a top position in this strenuous sport activity Nevertheless it has been noted that deeply inverted T waves regularly have been present in multiple limb and precordial leads of his routine 12 lead ECG even though physical examination and conventional radiologic studies did not disclose any evidence of structural cardiac disease Observations were also made with respect to the ECG response to exercise and these proved to be somewhat comparable to ours. Thus it was found that the T waves became normally upright in all leads following a period of especially strenuous exercise whereas they remained abnormal after a double Master two step test It is especially noteworthy that the extent of the exercise determined the mutability of the T waves This experience suggests that the T wave abnormalities in 3 of our cases might not have persisted if we had utilized an exercise test which involved a work load in excess of the 150 watts for 3 minutes as was customarily employed

Similar ECG abnormalities have been noted occasionally in top-ranking athletes of other nationalities as well In this connection we allude to the publications of Venerando and Rulli[15] and of Dembo[16] The former authors had conducted an ECG survey in 69 marathon runners and 38 marathon walkers who had participated in the Olympic games in Rome in 1960 The authors had been impressed by the high incidence of T wave abnormalities in the resting ECG s. However when we carefully reviewed their data it became apparent that the abnormalities we have described in the ECG s of our group of athletes matched in only one instance those present in the ECG s of their sample Moreover they did not provide an explanation for this ECG phenomenon and merely identified it as an indication of an anomaly of the repolarization phase unrelated to an organic myocardial lesion In support of this view they cited the regular occurrence of an inverted T wave in Lead II despite a record of outstanding athletic performance for many years on the part of a young professional basketball player in South America whom they had personally followed over this period of time

On the other hand Dembo[16] whose observations were confined to a limited sample of top-ranking Russian athletes, had come to a different conclusion He had noted the presence of T wave inversions in multiple leads of athletes resting ECG s when they were in top condition and also disappearance of these ECG changes when the training was temporarily interrupted On the basis of this experience he presented a somewhat unorthodox theory in order to account for the abnormal ECG s Thus, he postulated that the achievement of a state of peak physical condition through exercise will at the same time be associated with the development of a level of sympathicotonia sufficient to produce structural albeit reversible myocardial lesions as well Accordingly his approach has been to characterize the T wave inversions in the ECG s of top-ranking athletes as an expression of some structural myocardial abnormalities and he has not considered them to be a benign ECG phenomenon However it seems to us that it is difficult to reconcile such an interpretation first with the behavior of the T waves in the ECG s of our athletes following an exercise test and second with their record of outstanding physical performance despite the persistence of T wave inversions in repeated routine ECG s.

Admittedly we do not as yet have sufficient data which would permit us to provide a satisfying alternative explanation for the occurrence of striking T wave abnormalities in the resting ECG s of the segment of top-ranking athletes we have examined and whose record of performance has been equal to or even greater than those whose resting ECG s were normal We suspect that there may be a neuro-

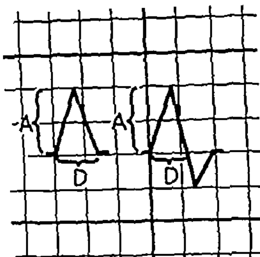


Fig. 1 Derivation of the IPI Amplitude (A) × duration (D) = IPI in mm. per second.

right ventricular systolic pressure range was 26 to 177 mm. Hg the mean was 78 mm. Hg In 14 patients one third of the total the pressure range was 26 to 52 mm Hg in another 14 it was 55 to 85 mm. Hg and in the remaining third 88 to 177 mm Hg

Four of the 43 patients with TET had pulmonary atresia rather than stenosis. In 17 of the 43 a systemic pulmonary shunt operation of either the Blalock Taussig (13) or Potts (4) type had been done prior to obtaining the electrocardiograms studied. Four of the 17 shunts were nonfunctioning at the time of study eight were probably inadequate on the basis of clinical findings, four were judged adequate and only one was thought to be too large

Method

Standard 12 lead tracings of both normal and patient groups were completed using several direct-writer Sanborn or Hewlett Packard recorders. Several technicians obtained the tracings, which were recorded using paper speed and sensitivity of 25 mm. per second, and one mv = 10 mm. respectively

The following observations and measurements were made in all tracings the lead containing the P wave of maximal amplitude (P_{max}) and its magnitude in millimeters abnormality in P wave configuration morphology of the P wave in Leads V and V and amplitude and duration of the positive and negative components of the P wave in Lead V_1 In addition the product of amplitude and duration of the positive portion of I V_1 was also determined this latter product called the initial P V_1-index (II I) was derived as shown in Fig 1 Fiftieth ninetieth and ninety-fifth percentile values of P_{max} and II I were determined. The ninetieth percentile values were arbitrarily chosen as the criteria by which RAA could be assessed in the patient group. This percentile is an acceptable top-normal value in spite of the fact that there is necessarily a 10 per cent loss of specificity with its use it has previously been used and explained by others.[6,9] Ninety-fifth percentile values are also reported and may be used to insure greater specificity but some instances of true RAA may not be diagnosed

Certain statistical comparisons, as indicated by p values, were made by the χ^2 method Yates correction was used where necessary Linear quadradic, and cubic models analyzed by computer were used for multiple regression analysis of both P_{max} and IPI versus pulmonary to-systemic flow ratio (Qp/Qs) right ventricular systolic pressure (RVp) and cardiothoracic (C/T) ratio obtained from the chest x ray in patients with ASD and versus RVp only in patients with PS. In patients with TET no regression analyses were done. Linear discriminant analysis of P_{max} and IPI in normal children versus patients with right-sided overload was used to determine a discriminant function which could be used to separate these two groups into those with and without RAA. No electrocardiograms of normal infants, or of patients less than one year of age, were used in this comparison since few (eight) of the patients were infants. Thus, the electrocardiograms of 120 patients, all older than one year of age were compared with those of the 51 normal children 4 to 12 years of age. Discriminant functions were then chosen so that 90 per cent and 95 per cent, respectively of normal children would be classified as normal.

Results

Normal group P_{max} data are found in Table I P_{max} declined with age during

The electrocardiographic recognition of right atrial abnormality in children

James L Reynolds M.D
New Orleans La

The electrocardiographic diagnosis of right atrial abnormality (RAA) can be made relatively infrequently even in patients with known right atrial overload Available diagnostic criteria are less certain and well defined than those of left atrial abnormality [1-3] and diagnostic methodology seems to have been somewhat neglected Because of this situation a study of the P wave relative to RAA was made and is the subject of this report Particular attention was paid to the P wave in Lead V_1 and certain hemodynamic factors to which RAA may be etiologically related were investigated The term abnormality in reference to the right atrium rather than hypertrophy dilatation enlargement or overload is used to avoid the unwarranted specificity connoted by these other terms. From the study new more sensitive diagnostic criteria of RAA were derived

Study groups

Normal group The P wave was analyzed in 199 electrocardiograms obtained from normal children of various ages These children were subgrouped as follows premature or low birth weight infants (PNB) 50 normal weight or term newborn infants (TNB) 22 one month-old infants (1 mo) 26 9 to 12 month-old infants (9 to 12 mo) 50 and 4 to 12 year old children (4 to 12 yr) 51 Normal values for certain P wave measurements were established for each subgroup. Other data derived from the 199 tracings, the recording technique used and a detailed description of the infants and children studied were previously reported [4]

Patient group Tracings obtained from 128 patients with right-sided cardiac overload due to either atrial septal defect (ASD) pulmonic stenosis (PS) or tetralogy of Fallot (TLT) were also analyzed

The diagnosis in every patient was substantiated by cardiac catheterization The age range was 8 weeks to 16 years eight patients were less than one year of age 71 were 1 to 3 years of age six were more than 12 years of age and of these five were 13 years of age

Of 43 patients with secundum or sinus venosus type ASD eight had partial anomalous pulmonary venous connection three others had associated anatomic pulmonary artery coarctation or stenosis. The pulmonary to-systemic flow ratio range in ASD patients was 1 2 to 5 8 the mean was 2 66 in 11 the range was 1 2 to 1 9 in 19 it was 2 1 to 2 9 and in 13 it was 3 0 to 5 8 The right ventricular systolic pressure range in ASD patients was 16 to 76 mm Hg the average was 38 mm Hg

The ventricular septum was intact in the 42 patients with PS and none had a left to right or right to-left shunt. The

From the Departments of Pediatrics and Surgery Tulane University School of Medicine, New Orleans, La.
Received for publication July 20, 1970.
Reprint requests to Dr Reynolds, 1430 Tulane Avenue, New Orleans, La. 70112.

June 1971 Vol. 81 No. 748-759

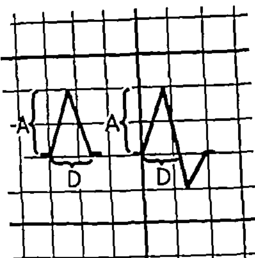


Fig. 1 Derivation of the IPI Amplitude (A) × duration (D) = IPI in mm. per second.

right ventricular systolic pressure range was 26 to 177 mm. Hg the mean was 78 mm. Hg in 14 patients, one third of the total the pressure range was 26 to 52 mm Hg, in another 14 it was 55 to 85 mm. Hg and in the remaining third 88 to 177 mm Hg.

Four of the 43 patients with TET had pulmonary atresia rather than stenosis. In 17 of the 43 a systemic-pulmonary shunt operation of either the Blalock Taussig (13) or Potts (4) type had been done prior to obtaining the electrocardiograms studied Four of the 17 shunts were nonfunctioning at the time of study eight were probably inadequate on the basis of clinical findings, four were judged adequate, and only one was thought to be too large.

Method

Standard 12-lead tracings of both normal and patient groups were completed using several direct writer Sanborn or Hewlett Packard recorders. Several technicians obtained the tracings, which were recorded using paper speed and sensitivity of 25 mm per second and one mv = 10 mm respectively

The following observations and measurements were made in all tracings the lead containing the P wave of maximal amplitude (P_{max}) and its magnitude in millimeters abnormality in P wave configuration morphology of the P wave in Leads V and V and amplitude and duration of the positive and negative components of the P wave in Lead V_1 In addition the product of amplitude and duration of the positive portion of I V_1 was also determined this latter product, called the *initial P V_1 index* (IPI) was derived as shown in Fig 1 Fiftieth ninetieth and ninety-fifth percentile values of P_{max} and IPI were determined The ninetieth percentile values were arbitrarily chosen as the criteria by which RAA could be assessed in the patient group This percentile is an acceptable "top-normal value in spite of the fact that there is necessarily a 10 per cent loss of specificity with its use it has previously been used and explained by others.[4] Ninety fifth percentile values are also reported and may be used to insure greater specificity but some instances of true RAA may not be diagnosed.

Certain statistical comparisons, as indicated by p values, were made by the χ^2 method Yates correction was used where necessary Linear quadradic, and cubic models analyzed by computer were used for multiple regression analysis of both P_{max} and IPI versus pulmonary to-systemic flow ratio (Qp/Qs) right ventricular systolic pressure (RVp) and cardiothoracic (C/T) ratio obtained from the chest x ray in patients with ASD and versus RVp only in patients with PS In patients with TET no regression analyses were done. Linear discriminant analysis of P_{max} and IPI in normal children versus patients with right-sided overload was used to determine a discriminant function which could be used to separate these two groups into those with and without RAA. No electrocardiograms of normal infants, or of patients less than one year of age, were used in this comparison since few (eight) of the patients were infants. Thus, the electrocardiograms of 170 patients, all older than one year of age were compared with those of the 51 normal children 4 to 12 years of age. Discriminant functions were then chosen so that 90 per cent and 95 per cent, respectively of normal children would be classified as normal.

Results

Normal group P_{max} data are found in Table I. P_{max} declined with age during

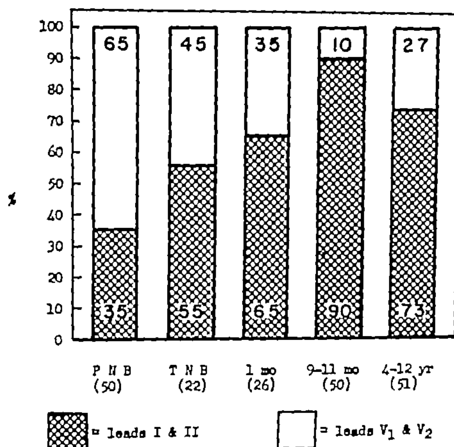


Fig 2 ECG-lead location of P_{max} in 199 normal tracings from children of various ages. Age groups are as defined in the text; the number of tracings examined in each age group appears in parentheses.

Table I P_{max} of normal infants and children

Age group	No	Mean	50%	90%	95%	Max
PNB	50	1.61	1.5	2.0	2.5	3.0
TNB	22	1.56	1.5	2.0	2.0	2.75
1 mo.	26	1.44	1.5	2.0	2.0	2.0
9 to 12 mo.	50	1.20	1.0	1.75	2.0	2.0
4 to 12 yr	51	1.13	1.0	1.5	1.5	2.0
All ages	199	1.36	1.25	2.0	2.0	3.0

Age groups and P_{max} are defined in the text. Amplitudes are in millimeters—1 mv = 10 mm. 50%, 90%, and 95% are percentile values. Max = height of tallest P_{max}.

infancy this decline was statistically significant p = <0.01. Although low birth weight newborn infants seemed to have somewhat taller P waves than normal weight newborn infants the difference was not statistically significant p = <0.77. In only four (2 per cent) of the 199 tracings was P_{max} ≥ 1.5 mm; all four were tracings of low birth weight neonates. A P_{max} of 3 mm was found only once. The ninetieth percentile value for P_{max} during the first month of life was 2.0 mm; in older infants it was 1.75 mm, and in children a P wave as high as 2 mm was found in only two instances (4 per cent).

The P_{max} was located in standard Lead II in 62 per cent of 199 tracings, in Lead V_2 in 22 per cent, in Lead V_1 in 13 per cent, and in Lead I in 3 per cent; it was found in Leads aV_L and V_4 in 0.5 per cent each. As seen in Fig 2, the P_{max} in neonates was frequently found in the right precordial

Table II Initial P V measurements of normal infants and children

Age group	No.	P V amplitude (mm.)	P V duration (sec)	IPI (mm sec.)	Percentile
PNB	50	1 0	0 03	0 04	50%
		1 0	0 04	0 075	90%
		1 0	0 05	0 08	95
		1 5	0 05	0 10	Max
TNB	22	1 0	0 04	0 045	50%
		1 5	0 05	0 075	90%
		1 75	0 06	0 075	95
		2 0	0 06	0 08	Max
1 mo.	26	0 75	0 03	0 03	50%
		1 25	0 04	0 05	90%
		1 5	0 04	0 06	95%
		1 5	0 04	0 06	Max
9 to 12 mo.	50	0 5	0 03	0 03	50%
		1 0	0 04	0 04	90%
		1 0	0 04	0 04	95%
		1 0	0 04	0 04	Max
9 to 12 y	51	0 75	0 04	0 04	50%
		1 0	0 06	0 05	90%
		1 25	0 07	0 06	95
		1 5	0 07	0 06	Max
All age groups	199	0 75	0 04	0 03	50%
		1 5	0 05	0 06	90%
		1 75	0 06	0 07	95%
		2 5	0 07	0 10	Max

Age groups are defined in the text, IPI Initial P V index, No. = number in each age group, P V the P in Lead V

leads, while in children it was usually found in standard Leads I and II If the neonatal groups are combined n 58 per cent P_{max} is in the right precordial leads.

Data relative to the positive portion of the P wave in Lead V appear in Table II Amplitude of P V noticeably higher in the newborn period declined during the first year of life and remained lower during the remainder of childhood In contrast, the positive P V duration increased after the first year of life The IPI while larger in the newborn period—ninetieth percentile = 0 075 mm sec —was relatively constant—ninetieth percentile = 0.05 mm. per second—during the remainder of childhood. There was a significant ($p = <0.01$) decline in IPI and in positive P V voltage during infancy

Morphologic data relative to the P wave in Leads V and V were previously published. No statistically significant relationship was demonstrated between a diphasic P V_1 configuration and age among the different age groups the incidence of diphasic configuration varied from 43 to 74 per cent the average was 61 per cent.

The ninetieth and ninety-fifth percentile values of both P_{max} and IPI appear in Table III The ninetieth percentile values were used as criteria by which to assess RAA in the patient group.

Patient group The percentages of patients with P_{max}, IPI either of these or both exceeding the respective ninetieth percentile normal values for age (Table III) appear in Table IV and Fig 3 In about one half or more of each patient subgroup there was evidence of RAA. P_{max} and IPI were found to be equi-sensitive indicators of RAA. One measure exceeded the ninetieth percentile while the other did not with about equal frequency and in an appreciable number of patients (Table V)

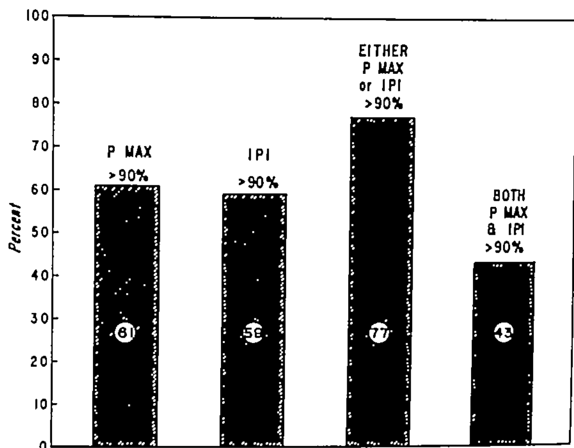


Fig 3 Diagnosis of RAA in 128 patients with either ASD PS, or TET by P_{max}, IPI either of these, or both >90th percentile for age, respectively

If the criterion for diagnosis of RAA be that either P_m or IPI is greater than the respective normal ninetieth percentile RAA is diagnosed more frequently than if the criterion be that both are positive Diagnostic specificity is increased in the latter instance however since among the 199 normal tracings there was none in which both P_{max} and IPI were greater than the respective ninetieth percentile for age

In Fig 4 a comparison is made of the frequency with which RAA was diagnosed in the *same* patients on the basis of diag nostic method By using the criterion of either P_{max} or IPI > ninetieth percentile for age, RAA was found with significantly ($p = < 0.01$) greater frequency than by using the conventional criterion $P > 2.5$ mm Only 19 per cent of the 128 patients had RAA on the basis of $P > 2.5$ mm while 77 per cent of the same patients had RAA on the basis of the new criteria. In 43 per cent of the patient group both P_{max} and IPI were greater than ninetieth per centile.

Linear discriminate analysis of P_{max} and IPI in normal children (4 to 12 years of age) versus patients (greater than one year of age) with right-sided overload yielded the following equation

$$Z = P_m \quad (-0.009) + IPI\ (-0.024)$$

In this equation Z is the discriminant function and P_{max} and IPI as previously defined are the discriminant function coefficients. When Z was chosen so that

Table III Criteria for diagnosis of RAA P_m or IPI > the ninetieth or ninety-fifth percentile normal value for age

Measure	*Age groups*	*90th percentile*	*95th percentile*
		(mm.)	(mm.)
P_m	NB to 1 mo.	2 0	2 5
	> 1 mo. to 1 yr	1 75	2 0
	> 1 yr	1 5	1 5
		(mm sec.)	(mm sec.)
IPI	NB to 1 mo.	0 075	0 08
	> 1 mo.	0 05	0 06

NB = Newborn infant; 1 mo. = one month of age; 1 yr. = one year of age; P_{max} and IPI are defined in the text.

Table IV. Frequency with which P_{max} and IPI exceeded the ninetieth percentile in 128 patients with either ASD, PS, or TET

Patient subgroup	No.	P > 90% (%)	IPI > 90% (%)	P or IPI > 90% (%)	Both P and IPI > 90% (%)
ASD	43	53	49	74	28
PS	42	45	52	64	33
TET	43	84	74	91	67
Total	128	61	59	77	43

90% = 90th percentile. Other abbreviations are defined in the text.

Table V. IPI versus P_{max} as the sole indicator of RAA

Patient subgroup	IPI > 90%, P < 90% No.	%	P > 90%, IPI < 90% No.	%
ASD	9	28	11	34
PS	8	30	5	19
TET	3	1	7	2
Total	20	22	23	23

90% = 90th percentile. Other abbreviations are as previously defined.

90 per cent or 95 per cent, respectively, of normals were correctly identified as normal: $Z^{90\%} = -0.0143$ and $Z^{95\%} = -0.0151$. If $Z^{95\%}$ is < (more negative than) -0.015, there is > a 95 per cent chance of RAA. A histogram based on linear discriminant analysis of P_{max} and IPI data from normal and patient groups is seen in Fig. 5. These data appear in different form in Fig. 6 in which the application of the *discriminant function* chosen at either the ninetieth or ninety-fifth percentile level, to normal and patient groups is depicted.

The P wave in Lead V_1 was diphasic (+/−) in 47 per cent of the patients with ASD and 58 per cent of those with TET (Table VI). These percentages are within the normal range indicated in the preceding section. In patients with PS, however, P V_1 was diphasic in only 14 per cent. The difference in incidence is significant, p = < 0.01. Only one of the six PS patients with a diphasic P V_1 was among those with RVp equal to, or above, the systemic pressure level.

The terminal negative P V_1 deflection was *larger than the initial* positive deflection in four of those patients with ASD, in none of those with PS, and in one with TET. Although the *terminal* P V_1 index (TPI)[4] exceeded the ninetieth percentile value, 0.015 mm. sec., in 15 patients, in *only three, all with ASD*, was the terminal P V_1 duration > 0.04 sec. The terminal P V_1 deflection had a slow ascent or was coved as in left atrial enlargement, in four of the seven ASD patients with TPI > 0.015 *mm.* sec., and acuminated or V-shaped in the other three. *In all PS or TET patients with a* prominent terminal P V_1 *component, this* deflection was V-shaped. The P wave in Lead V_2 in such patients was usually positive, peaked, and tall. The *abnormal TPI* in the seven TET patients can not be attributed to *too* large a systemic-pulmonary shunt. In two of the seven there was no shunt, in another two it was nonfunctioning, in two more it was judged inadequate, and in the remaining patient it was of "adequate" size.

That by either old *or new criteria* RAA was found more frequently (Fig. 4) in those patients with TET than in those with either ASD or PS raises *the question of* what type and degree of atrial overloading cause P wave *changes*. Linear, quadratic, and cubic models of regression analyses were used to determine possibly significant associations between P_{max} or IPI and Qp/Qs, RV_p, and C/T ratio, as defined

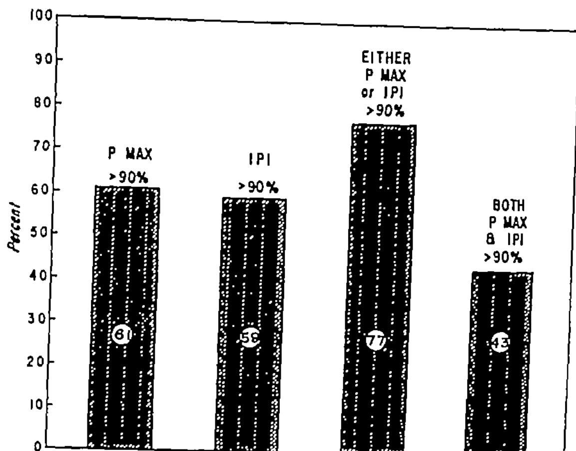


Fig. 3 Diagnosis of RAA in 128 patients with either ASD PS, or TET by P_m IPI either of these, or both >90th percentile for age respectively

If the criterion for diagnosis of RAA be that either P_m or *IPI* is greater than the respective normal ninetieth percentile RAA is diagnosed more frequently than if the criterion be that both are positive Diagnostic specificity is increased in the latter instance however since among the 199 normal tracings there was none in which both P_{max} and IPI were greater than the respective ninetieth percentile for age

In Fig 4 a comparison is made of the frequency with which RAA was diagnosed in the *same* patients on the basis of diag nostic method By using the criterion of either P_{max} or IPI > ninetieth percentile for age RAA was found with significantly ($p = < 0.01$) greater frequency than by using the conventional criterion $P > 2.5$ mm Only 19 per cent of the 128 patients had RAA on the basis of $P > 2.5$ mm while 77 per cent of the same patients had RAA on the basis of the new criteria. In 43 per cent of the patient group both P_{max} and IPI were greater than ninetieth per centile

Linear discriminate analysis of P_{max} and IPI in normal children (4 to 12 years of age) versus patients (greater than one year of age) with right sided overload yielded the following equation

$$Z = P_m \quad (-0.009) + IPI\ (-0.024)$$

In this equation Z is the discriminant function and P_{max} and IPI as previously defined are the discriminant function coefficients. When Z was chosen so that

Table III Criteria for diagnosis of RAA P_m or IPI > the ninetieth or ninety fifth percentile normal value for age

Measure	Age groups	90th percentile	95th percentile
		(mm.)	(mm.)
P_m	NB to 1 mo.	2.0	2.5
	> 1 mo. to 1 yr	1.75	2.0
	> 1 yr	1.5	1.5
		(mm sec.)	(mm. sec.)
IPI	NB to 1 mo.	0.075	0.08
	> 1 mo.	0.05	0.06

NB = Newborn infant; 1 mo. = one month of age; 1 yr = one year of age; P_{max} and IPI are defined in the text.

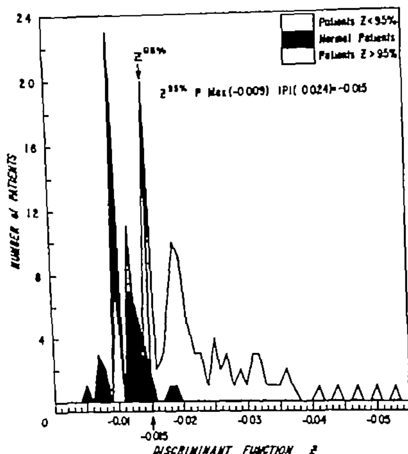


Fig. 5 Histogram based on linear discriminant analysis of P and IPI data from normal children and from children more than one year of age with either ASD, PS, or TET

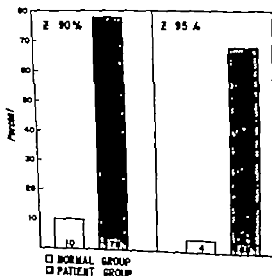


Fig. 6 Diagnosis of RAA in normal and patient groups by Z value in excess of the ninetieth (−0.0143) or ninety-fifth (−0.0151) percentile, respectively. Only children older than one year of age are in the patient group; only those 4 to 12 years of age are in the normal group.

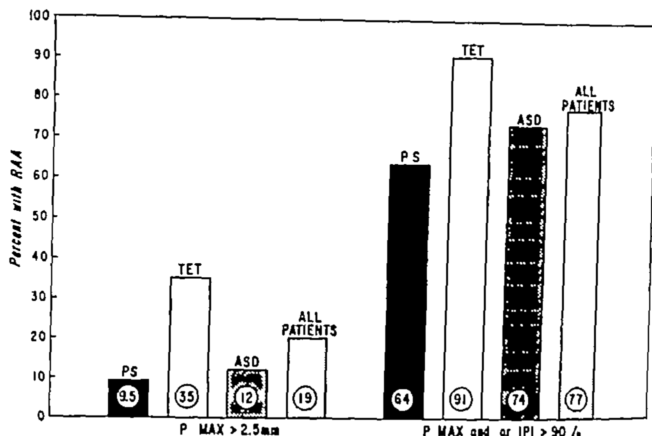


Fig. 4 Diagnosis of RAA in 128 patients with either ASD PS or TET by conventional versus new diagnostic method P_{max} > 2.5 mm versus P_{max} and/or IPI >90th percentile for age.

Table VI Terminal P V_1 deflection in patient group morphology and measurement data

Diagnosis	*Morphology*		*Initial vs terminal size*			*T P V_1-index >0.015 mm sec*	*T P V_1 duration >0.04 sec.*
	+/−	+	>/<	=/=	</>		
ASD	20	23	15	1	4	7	3
PS	6	36	5	1	0	1	0
TET	25	18	23	1	1	7	0

P V = P wave in Lead V_1; +/ − = diphasic P V; + = positive P V; >/< = terminal P V deflection greater than initial deflection; =/= = terminal P V deflections of equal size; </> = terminal P V deflection less than initial deflection; T P V index = terminal P V index = amplitude × duration of terminal deflection T P V duration = duration of the terminal P V deflection.

previously The p values obtained from these multiple regression analyses appear in Table VII In patients with ASD only one equivocally significant relationship $p = <0.05$ was found that between C/T ratio and IPI Neither IPI nor P_{max} was significantly related to RVp and Qp/Qs in patients with ASD In patients with PS both P_{max} and IPI were significantly related to RVp—primarily in the linear and quadratic models. This relationship between RVp and both P_{max} and IPI is emphasized further by the fact that 86 per cent of the 14 patients with RVp at systemic pressure level or above (88 to 177 mm Hg) had RAA An almost equivalent percentage 91 per cent of patients with TET also had RAA

Discussion

The electrocardiographic diagnosis of RAA depends essentially on the presence of a tall P wave the major criterion for diagnosis of RAA A decreased *P/PR* segment ratio which was suggested as a sign of RAA was found to be unreliable [5,6]

evidence of this underdiagnosis. The results of this study indicate that lower age-related, amplitude values should be used as criteria by which RAA is diagnosed. Such values are the ninetieth and ninety fifth percentile values in Table III.

Since the vector of left atrial depolarization is usually perpendicular to the Lead V axis, or is even more posteriorly rotated, the positive portion of P V_1 is essentially due to right atrial depolarization.[23,24] The IPI is considered an area-estimate of right atrial depolarization in the horizontal plane. IPI was found to be as sensitive in detection of RAA as P_{max}. In about 20 per cent of the patients with IPI > ninetieth percentile, the P_{max} was within normal limits, and IPI provided the only indication of RAA (Table V). These data support its use in the assessment of RAA and when used in conjunction with P_{max} over three quarters of the patients studied had evidence of RAA (Fig. 3).

By combining both P_{max} and IPI into a single formula—$Z^{90\%} = P_{max}(-0.009) + IPI(-0.024) = -0.014$—they can be simultaneously applied in the assessment of RAA. When this was done in the case of patients with right-sided overload, over three quarters of them had evidence of RAA (Fig. 6). In comparison with use of P > 2.5 mm. as the criterion of RAA, sensitivity is increased three to four times and yet specificity is 90 per cent. This can be increased to 95 per cent by using $Z^{95\%} = -0.015$. When this was done, almost 70 per cent of the patients still had evidence of RAA (Figs. 5 and 6).

Certain features of the terminal portion of P V_1 in patients with right-sided overload deserve comment. Its absence in 86 per cent of the patients with PS may in itself have diagnostic value, since a terminal negative deflection is frequently found in normal children and in those with ASD or TET (Table VI). A prominent terminal negative component may be found in patients with exclusively right-sided overload; it is not limited entirely to those with left atrial enlargement. Certain features usually distinguish it, however, from that associated with left atrial enlargement. These are an acuminated shape and a duration ≥ 0.04 sec. With left atrial enlargement the terminal P V_1 component is typically rounded or coved and usually > 0.04 sec. duration. There are however exceptions to these generalizations. Of additional help in determining whether a prominent negative P V_1 deflection is due to right or left atrial abnormality is the occurrence of a peaked tall P V_2 in patients with RAA. If features suggestive of right and left atrial abnormality exist, biatrial abnormality should be considered. This is suspected in some of the patients with ASD with a prominent terminal P V_1 component. Two of these had evidence of left atrial enlargement in standard Lead I. P wave changes with combined right and left atrial abnormality deserve further study.

The cause of P wave changes with right atrial overload is uncertain. Right atrial hypertrophy or enlargement, increased right atrial pressure, outflow obstruction and volume overloading of the right atrium are evident possible causes. The term right atrial abnormality, RAA, was chosen because of its nonspecificity. In this study neither P_{max} nor IPI could be related to size of left-to-right shunt in patients with ASD. Sanchez-Cascos and Deuchar[26] also found no such correlation but did find that P duration and upstroke time were related to shunt volume. In patients with ASD, P wave changes were reported to be unrelated to right atrial pressure,[26,27] right ventricular pressure, or atrial size as determined angiographically.[28] In this study neither was any definite relationship found with cardiothoracic ratio or right ventricular systolic pressure. Right ventricular systolic pressure was positively correlated, however, with both P_{max} and IPI in patients with pulmonary stenosis; this correlation was previously demonstrated.[29] Increasing right ventricular systolic pressure could decrease right ventricular compliance and thereby increase resistance to right atrial emptying, or could possibly cause, by stimulating right ventricular hypertrophy, a rightward shift in right atrial position. Such a shift may also explain the predominantly positive P configuration in Lead V_1 in PS patients, but one wonders why a similar shift does not occur in patients with TET. P ampli-

Table VII. P_{max} and PPI versus Qp/Qs, C/T, and RVp: multiple regression analysis

Variables		Linear		Quadratic		Cubic	
		P_{max}	PPI	P_{max}	PPI	P_{max}	PPI
ASD	Q_p/Q_s	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
(13)	C/T	>0.05	<0.05 >0.01	>0.05	<0.05 >0.01	>0.05	>0.05
	RV_p	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
PS (42)	RV_p	<0.01	<0.01	<0.01	<0.01	<0.01	<0.05 >0.01

Linear, quadratic, and cubic refer to the statistical models used. Other terms are defined in the text.

Peaking of the P wave is a somewhat imprecise measure; it can be found normally in young infants and is influenced by heart rate. The slope of the ascending limb of the P wave is useful but difficult to apply routinely. Since increased amplitude is critical in the diagnosis of RAA, it is desirable that factors influencing it and the limits of normal be carefully defined.

P amplitude may be depressed by inadequate frequency response of the recorder. Direct writer recorders such as those used in this study are especially suspect.[19] However, depression of P, a relatively slow deflection, is much less likely than that of QRS and is probably not clinically significant if current frequency response standards are met. Extracardiac factors which may increase P amplitude should also be considered. Inspiration, the Valsalva maneuver, adrenergic stimulation, exercise, hypocalcemia, hypoxia, and hyperthyroidism are the major ones.[11] Additionally, this study indicates that age is yet another amplitude-determining factor which should be recognized. Right ventricular compliance and its relation to age may be relevant. Normally the tallest P waves occur in the smallest and youngest babies. Others[11,8] have observed that premature or low birth weight neonates apparently have even taller P waves than those of normal weight and gestation. This tendency was observed in this study also, but the difference was not validated statistically; perhaps with larger groups of normal and low birth weight neonates this would be possible. P waves in the adult are reported to be of lower amplitude than in children. That P amplitude is age-dependent and greater during infancy has apparently not been generally recognized.[1,11,14] One of the reasons for this perhaps is early neglect of the right precordial leads in determining P_{max}. In a large percentage of infants P_{max} is found in these leads (Fig. 2), and the shift in P_{max} with age from the horizontal to the frontal plane may have been overlooked.

It is stated in most, if not all, current pediatric cardiology texts that the criterion by which right atrial hypertrophy can be diagnosed is a P wave taller than 2.5 mm[11,17,18] or 3.0 mm.[1,11,19,20] Few large studies of P amplitude have been done, however, and apparently great reliance has been placed on Ziegler's maximal value of 2.5 to 3.0 mm in determining this criterion of abnormality.[11] In the present study only a rare newborn infant had P waves this tall. Data from this study indicate that it is unreasonable to require for diagnosis of RAA that a maximal value be exceeded—found only in neonates be exceeded—especially since very small increases in amplitude may be extremely significant in the case of relatively low amplitude deflections such as P waves. That only 19 per cent (Fig. 4) of the 138 patients in this study with right-sided overload had RAA by the criterion of a P wave in excess of 2.5 mm, while 61 per cent (Fig. 3) of the *same* patients had RAA by the criterion of a P_{max} > ninetieth percentile for age is [illegible]

13. Wenger N. K., Watkins, W. L., and Hurst, J. W. A preliminary study of the electrocardiogram of the normal premature infant, Amer. Heart J 62:304 1961.
14. Ziegler R. F. Electrocardiographic studies in normal infants and children, Springfield, Ill., 1951 Charles C Thomas, p. 37
15. Walsh, S. Z. Electrocardiography in infants and children, Watson, H., editor: Pediatric cardiology St. Louis, 1968, The C. V. Mosby Company p. 127
16. Liebman, J. Electrocardiography, Moss, A. J. and Adams, F. H., editors: Heart disease in infants, children, and adolescents, Baltimore, 1968, The Williams & Wilkins Company, p. 220.
17. Nadas, A. S. Pediatric cardiology ed. 2, Philadelphia, 1963, W. B. Saunders Company p. 57
18. Namin, E. P. Pediatric cardiography and vectorcardiography, in Gasul, B. M. Arcilla, R. A., and Lev M., editors. Heart disease in children, Philadelphia, 1966, J. B. Lippincott Company p. 112.
19. Green, E. W. The normal P wave, in Cassels, D. E., and Ziegler R. F. editors Electrocardiography in infants and children, New York, 1966, Grune & Stratton, Inc., p. 111.
20. Krovetz, L. J. Gessner I. H. and Schiebler G. L. Handbook of pediatric cardiology New York, 1969 Harper & Row Publishers, p. 81.
21. Keith, J. D., Rowe, R. D. and Vlad, P. Heart disease in infancy and childhood, New York, 1967 The Macmillan Company p. 42.
22. Guntheroth, W. G. Pediatric electrocardiography Philadelphia, 1965 W. B. Saunders Company p. 78.
23. Wenger R., and Hofmann-Credner D. Observations on the atria of the human heart by direct and semidirect electrocardiography Circulation 5:870, 1952.
24. Reynolds, G. The atrial electrocardiogram in mitral stenosis, Brit. Heart J 15:250, 1953.
25. Sanchez-Cascos, A., and Deuchar D.: The P wave in atrial septal defect, Brit. Heart J 25:202, 1963.
26. Oliveira, J. M. and Zimmerman, H. A.: The electrocardiogram in interatrial septal defect and its correlation with hemodynamics, Amer. Heart J 55:369 1958.
27. Oliveira, J. M. and Zimmerman, H. A. Auricular overloadings. Electrocardiographic analysis of 193 cases, Amer J Cardiol. 3:453 1959
28. Anselmi, G. Munoz Armas, S., Salazar A., Anselmi, A., de Pisani, F. and Blanco, P. Electrocardiographic patterns of right atrial overloading in some congenital heart conditions, Amer J Cardiol. 21:628, 1968.
29. Sodi Pallares, D. and Calder R. M. New bases of electrocardiography St. Louis, 1956, The C. V. Mosby Company p. 255.
30. Gordon, R., Neilson, G., and Silverstone, H. Electrocardiographic P wave and atrial weights and volumes, Brit. Heart J 27 748, 1965

tude was related to right atrial pressure in patients with PS and tetralogy by others[27] but Anselmi and associates[24] did not find this association. In patients with tetralogy the significance of the relation of arterial unsaturation to P amplitude is also in doubt. While some investigators[27,28] found positive correlation, Anselmi[24] did not. Finally, in an autopsy study of adults by Gordon and co-workers[10] no correlation could be found between P amplitude and either right-atrial weight or volume. Thus the P wave changes are not attributable to any single factor. From this study, the relationship between P amplitude and right ventricular systolic pressure in patients with PS is definitely significant and perhaps of clinical value but no necessary etiologic significance can be implied.

Summary

P waves of normal children and of patients with either atrial septal defect (ASD), pulmonary stenosis (PS), or Fallot's tetralogy (TET) were analyzed and compared relative to right atrial abnormality (RAA). In the normal group P amplitude was consistently greater in infants. Normal P waves ≧ 2.5 mm were rarely (0.05 per cent) found but only in neonates. Maximal P amplitude (P_{max}) in 61 per cent of patients exceeded the ninetieth percentile age-related normal values but in only 19 per cent was $P > 2.5$ mm, the conventional criterion of RAA. The *initial P V_1 index* (IPI), a new measure of RAA obtained by multiplying positive P V_1 amplitude by duration, exceeded ninetieth percentile values in 59 per cent of patients and was *abnormal in 22 per cent of those* with a normal P_{max}. A formula in which IPI and P_{max} are combined was derived for assessment of RAA. By its use, 78 per cent of the patient group had evidence of RAA when diagnostic specificity was 90 per cent. In about 90 per cent of patients with TET either P_{max} or IPI was abnormal. In patients with PS P abnormality was found to be related to right ventricular systolic pressure. P waves in about 90 per cent of those with right ventricular pressure ≧ systemic pressure were abnormal. P V_1 was diphasic in the majority of those with TET but infrequently so in those with PS. Features useful in distinguishing sometimes prominent terminal negative P V_1 deflections of patients with RAA from those of patients with left atrial enlargement were found. In about three quarters of those with ASD either P_{max} or IPI was abnormal but P abnormality could not be related to either size of left-to-right shunt or height of right ventricular pressure.

It is concluded that sensitivity in the diagnosis of right atrial abnormality, whatever its cause, can be improved by use of criteria developed in this study while still maintaining acceptable diagnostic specificity.

REFERENCES

1. Zimmerman, H. A., Bersano, E. and Dicosky, C.: The auricular electrocardiogram, Springfield, Ill., 1968, Charles C Thomas, Publisher, p. 81.
2. Liebman, J.: Electrocardiography, *in* Moss, A. J., and Adams, F. H., editors: Heart disease in infants, children, and adolescents, Baltimore, 1968, The Williams & Wilkins Company, p. 219.
3. Derochers, A.: Atrial dilatation: electrocardiographic criteria, Un. Med. Canada 94:1023, 1965.
4. Reynolds, J. L.: The electrocardiographic recognition of left atrial enlargement in childhood, AMER. HEART J. 4:179, 1967.
5. Ziegler, M. M., Joseph, L. G., Nadas, A. S., and Massell, B. F.: The unipolar precordial and extremity electrocardiogram in normal infants and children, Circulation 4:420, 1951.
6. DePasquale, N. P., and Burch, G. E.: The electrocardiogram, ventricular gradient and spatial vectorcardiogram during the first week of life, Amer. J. Cardiol. 12:482, 1963.
7. Dixon, W. J., editor: Biomedical computer programs, Los Angeles, Sept. 1, 1965, University of California (Program BMD04M).
8. Gross, D.: Contributions to the functional morphology of the P wave, AMER. HEART J. 61:436, 1961.
9. Human, G. P., and Snyman, H. W.: The value of the Macruz index in the diagnosis of atrial enlargement, Circulation 27:935, 1963.
10. Dower, G. E., Moore, A. D., Ziegler, W. G., and Osborne, J. A.: On QRS amplitude and other errors produced by direct writing electrocardiographs, AMER. HEART J. 65:307, 1963.
11. Zimmerman, H. A., Bersano, E., and Dicosky, C.: The auricular electrocardiogram, Springfield, Ill., 1968, Charles C Thomas, Publisher, p. 31.
12. Hubsher, J. A.: The electrocardiogram of the premature infant, AMER. HEART J. 61:467, 1961.

11. Wenger N K, Watkins, W. L., and Hurst, J W A preliminary study of the electrocardiogram of the normal premature infant, AMER. HEART J 62:304 1961.
12. Ziegler R. F.: Electrocardiographic studies in normal infants and children, Springfield Ill 1951 Charles C Thomas, p. 37
13. Walsh, S. Z.: Electrocardiogr phy in infants and children, Watson, H., editor: Pediatric cardiology St. Louis, 1968, The C. V Mosby Company p. 127
14. Liebman, J: Electrocardiography Moss, A. J and Adams, F. H., editors. Heart disease in infants, children, and adolescents, Baltimore, 1968, The Williams & Wilkins Company p. 220.
17 Nadas, A. S Pediatric cardiology ed. 2, Philadelphia, 1963, W B Saunders Company p. 57
18. Namin, E. P Pediatric cardiography and ec torcardiography in Gasul, B. M Arcilla, R. A., and Lev M editors: Heart disease in children, Philadelphia, 1966, J B. Lippincott Company p. 112.
19 Green, E. W The normal P ve, Cassels, D. E and Ziegler R. F editors. Electrocardiography in infants and children, New York, 1966, Grune & Stratton, Inc., p. 111
20. Krovetz, L. J Gessner I H and Schiebler G. L. Handbook of pediatric cardiology New York, 1969 Harper & Row P blishers, p. 84.
21. Keith, J D., Rowe, R. D and Vlad, P Heart disease in infancy and childhood, New York, 1967 The Macmillan Company p. 42
22. Guntheroth, W G.: Pediatric electrocardiography Philadelphia, 1965 W B. Saunders Company p. 78.
23. Wenger R., and Hofmann-Credner D Observations on the tria of the human heart by direct and semidirect electrocardiography Circulation 5:870, 1952.
24. Reynolds, G. The atrial electrocardiogram in mitral stenosis, Brit. Heart J 15:250 1953.
25. Sanchez-Cascos, A., and Deuchar D The P w In atrial septal defect, Brit. H rt J 25:202, 1963.
26. Oliveira, J M., and Zimmerman, H. A. The electrocardiogram in inter-atrial septal defect and its correlation w th hemodynamics, A ER. HEART J 55:369, 1958.
27 Oliveira, J M and Zimmerman, H. A Auricular overloadings. Electrocardiographic analysis of 193 cases, Amer J Cardiol. 3:453 1959
28. Anselmi, G., M noz Armas, S., Salazar L., Anselmi, A de Pisani, F and Blanco, P Electrocardiographic patterns of right atrial overload ng in some congenital heart conditions, Amer J Cardiol. 21:628, 1968.
29 Sodi-Pallares, D and Calder R. M New bases of electrocardiography St. Louis, 1956, The C. V Mosby Company p. 253
30. Gordon, R., Neilson, G., and Silverstone, H. Electrocardiographic P ve and trial weight and olumes, Brit. Heart J 27 748, 1965.

Primary pericardial mesothelioma: Report of two cases and review of the literature

Alexander L. Sytman, M.D.
Rex N. MacAlpin, M.D.
Los Angeles, Calif.

It is now well established that mesotheliomas exist as distinct neoplasms.[1,2] Approximately 104 cases of primary pericardial mesothelioma have been reported in the world literature.[1,2,24] This subject was reviewed by Mahaim,[22] later by Dawe and co-workers,[1] and more recently by Mairot.[24] At most twenty-three of the cases reported were diagnosed before death,[4,9,14,20,22,24,23,25,27] and eleven of these have been discussed in Mairot's review.[24]

We have recently seen two patients with primary pericardial mesothelioma in whom the diagnosis was made ante mortem. One of these[18] has been previously reported upon in less detail. These patients are described here to emphasize that with currently available methods the diagnosis can be made during life.

Case reports

Case 1. In August, 1968, a 17-year-old Caucasian man developed the rather abrupt onset of steady pleuritic, aching anterior chest pain associated with progressive fatigue, fever, dyspnea on effort, orthopnea, occasional paroxysmal nocturnal dyspnea, and dependent edema. He was found to have distended neck veins, a left parasternal pulsation, and peripheral edema. There was mild cardiomegaly on x-ray and the electrocardiogram (ECG) was consistent with pericarditis. The white blood count (W.B.C.) was 10,500 with many atypical lymphocytes. Following a negative work-up for an infectious etiology, the patient was treated with antibiotics and steroids to which there was no response.

In November, 1968, the patient's venous pressure was 25 cm. H_2O and there was a paradoxical pulse of 35 mm. Hg. At that time a thoracotomy revealed serous effusions of about 1 L. in each pleural space. The pericardium, which was 7 to 8 mm. thick, was stony hard with no palpable heart action through it. It was stripped from the right ventricle and the anterior left ventricle. The epicardium was 3 to 4 mm. thick and almost cartilaginous. As much as possible was removed but, as it was stripped away, pieces of myocardium were seen attached to it. An optimal pericardiectomy was impossible. As a result of surgery the venous pressure fell from 40 to 15 cm. H_2O. During convalescence the patient sustained a right hemiparesis and aphasia followed later by subarachnoid hemorrhage. He continued to have fever of 100 to 101° F. but gradually regained neurologic function and fair exercise tolerance. However, his condition worsened again, and on Sept. 1, 1969, he was admitted to the UCLA Hospital. Examination revealed a blood pressure of 110/90 mm. Hg with a 5 mm. Hg paradoxical pulse and a heart rate of 108 beats per minute. There was no visible venous distension. There was a left parasternal systolic lift and a palpable pulmonic second sound. The cardiac apex was palpable in the anterior axillary line and a protodiastolic gallop was visible and palpable at the apex and lower sternal border. There was a Grade 2/6 systolic ejection murmur at the left sternal border and a pleuropericardial rub at the left sternal border and apex. Pulmonic closure was accentuated and the second sound was widely and almost

From the Department of Medicine, University of California School of Medicine, Los Angeles, Calif., and the Medical Service, Wadsworth Hospital, V.A. Center, Los Angeles, Calif.
Supported in part by United States Public Health Service Training Grant HE 1882? from the National Heart Institute.
Reprint requests to: Rex N. MacAlpin, M.D., Department of Medicine, UCLA Center for Health Sciences, Los Angeles, Calif. 90024.

 June, 1971, Vol. 81, No. 6, pp. 760-769



Fig. 1 Posteroanterior chest x-ray (Case 1) ith barium in the esophagus. There is slight cardiomegaly and straightening of the left heart border with elevation of the apex. The circular density overlying the base of the heart is metal suture from previous surgery

persistently split. A protodiastolic gallop or peri-cardial knock was audible t the pex and left sternal border The liver was palpable 5 cm below the right costal margin without pulsation. Except for slight residua of right hemiparesis the rest of the physical examination was normal.

Laboratory data included hemoglobin, 10.8 Gm. per cent; alkaline phosphatase, 25 King-Armstrong units (probably normal for his age) Bromsulphalein retention was 17.6 per cent in 45 minutes. Extensive studies failed to reveal viral, bacterial, or fungal etiology for his disease. The heart had an abnormal configuration on x-ray (Fig. 1) with an increase in the transverse diameter There was suggestion of right entricular hypertrophy on the lateral view The ECG (Fig. 2) showed sinus rhythm, right axis deviation, deep S waves in V and ST and T wave changes consistent with pericarditis. A cardiac blood pool scan ith technetium-99-labeled albumin showed significant separation of the intracardiac blood pool from the liver However there was no notable difference between the transverse diameter of the blood pool and the transverse diameter of the heart on roentgenogram.

Right heart catheterization and angiography ere performed on Sept. 2, 1969 Mean pulmonary artery edge pressure as 18 mm Hg. Pulmonary artery pressure as 35/16 mm. Hg with mean of 23. Right ventricular pressure as 35/0-12 mm. Hg and the tracing demonstrated configuration suggesting myocardial restriction (Fig. 3) Mean right atrial pressure was 12 mm. Hg and the tracing demonstrated the "M or "W" pattern characteristic of ventricular restriction with a/x = 15/10 and V/Y = 15/7 Brachial artery pressure as 106/55 mm. Hg and did not demonstrate paradoxical" pulse. Cardiac index measured by the indicator dilution technique was 3 45 L. per minute per square meter

A right atrial angiogram (Fig. 4) visualized both venae cavae, the right atrium, and the right ventricle. Abnormal wall thickness lateral to the right trium and abnormal separation of the heart from the diaphragm ere demonstrated. The right atrium as very small and contracted poorly Atrial filling was seen to end abruptly suggesting restrictive disease. The superior vena cava was constricted for 2 to 3 cm. near its entrance into the atrium. The right ventricle occupied its usual position and was not enlarged. The left ventricle was visualized on the levogram following injection of contrast medium into the main pulmonary artery All pulmonary arteries and veins were normal. The left atrium was small and contracted poorly The entire left ventricular chamber was elevated above its usual position and was the largest cardiac chamber Its diaphragmatic surface was rigid and contracted poorly Early diastolic filling ended abruptly The superior and lateral wall was deformed and bulged laterally and superiorly during diastole. This area contracted well during systole and probably represented that portion of the left ventricle which was rendered free of pericardial restriction in November 1968.

The slides of the pericardial lesion removed in November 1968, ere reviewed and it was made-

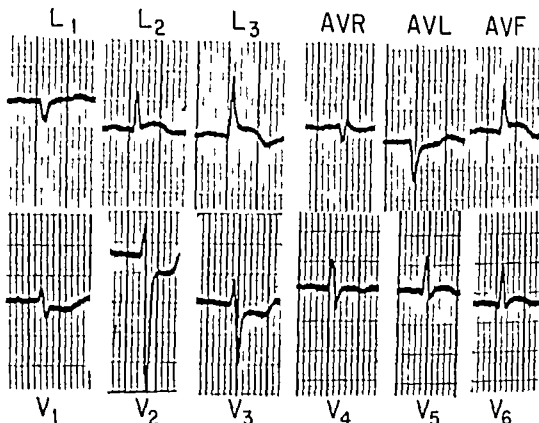


Fig. ECG (Case 1) taken on admission to UCLA Hospital. See text for discussion.

whether or not the lesion was neoplastic. On Sept. 29, 1969, the patient's chest was again surgically explored. Patchy tumor growth was found over the anterior surface of the heart. The tumor was extremely thick and extended inferiorly from both sides of the heart to invade the diaphragm. It surrounded the superior vena cava, extended posteriorly toward the spine, and laterally invaded the left lung. The right parietal pleura was dotted with multiple white nodules. There were no planes of dissection between the tumor and the heart. As much neoplasm as possible was removed from the anterior, the right, and the inferior surfaces of the heart. This did not change central venous pressure significantly.

Microscopic examination of the tumor (Fig. 5) disclosed a dense fibrous tissue presenting spindle-shaped cells with irregular vacuolated nuclei. In the same areas there were nests of cells that had a rather epithelial appearance. There were multiple areas where the spindle fibers were arranged in whorl-like fashion. In other areas there was a myxomatous appearance. Sections of the pleural nodules showed features similar to the abnormal pericardium. The pathologic diagnosis was pericardial mesothelioma.

The patient had a rapid postoperative recuperation and was sent home with dosages of diuretics and digoxin and melphalan, 2 mg. three times a day. His condition gradually worsened and he died with anasarca and cachexia in June, 1970.

Case . In July, 1965, a 43-year-old Caucasian man, who had previously been in good health, developed an acute episode of nocturnal dyspnea associated with constricting anterior chest pain, bilateral shoulder discomfort, diaphoresis, weakness, and a faint feeling. Discomfort was severe for 6 hours and persisted to a lesser degree for 2 weeks. It recurred 2 weeks later, and in August the third episode was associated with a blood pressure of 140/95 mm. Hg, an erythrocyte sedimentation rate of 53 mm. per hour (Wintrobe), and a hematocrit of 37 per cent. The patient was treated with antibiotics and prednisone with some relief. He had frequent night sweats and developed progressive shortness of breath, orthopnea, and episodes of dizziness which were not related to chest pain. In August he had a period of bilateral orchitis with thrombophlebitis in the right calf. In September he was found to have an enlarged heart on x-ray and was referred to the UCLA Hospital for diagnostic studies. Initial examination revealed a blood pressure of 155/110 mm. Hg without a paradoxical pulse, a regular heart rate of 100 beats per minute and a respiratory rate of 30 per minute. Distended cervical veins were not apparent. Over the right chest there were dullness and diminished breath sounds up to the angle of the scapula posteriorly. Coarse râles were heard at both lung bases and anterolaterally. There was a *left* parasternal lift. The heart sounds were soft. *There* was a protodiastolic gallop at the left sternal border and a Grade 2/6 systolic ejection murmur at the left upper sternal edge. The liver was palpable 1 cm. below the right costal margin and did not pulsate. The right calf was larger than the left but not tender. There was moderate left ankle edema.

Hemoglobin as 12 Gm. per cent. Extensive tests of renal and hepatic function ere normal. The patient remained afebrile and search for an infec tious cause of pericarditis was unrevealing. Chest x-rays (Fig. 6A) revealed massive heart which as globular. There as minimal pulmonary congestion and slight blunting of both costophrenic angles. An ECG (Fig. 7) showed low voltage in the limb leads, nonspecific S-T and T abnormalities, and first degree atrioventricular block. A cardiac blood pool scan (Fig. 6B) disclosed a ery small blood pool in relation to the roentgenologic heart size and significant separation of this pool from the diaphragm nd surrounding lung. T carbon dioxide angiograms were nondiagnostic nd several pericardiocenteses were dry in spite of recording epicardial potentials from the exploring needle. Right heart catheterization revealed mean pulmonary artery edge pressure of 30 mm. Hg. Pulmonary artery pressure was 45/30 mm. Hg ith mean pressure of 34 mm. Hg. Right ventricular pressure was 45/12 20 mm. Hg ith contour indicating restricti disease. Mean right atrial pressure was 17 mm. Hg.

A right atrial angiogram (Fig. 8) visualized the right trium, right ventricle, pulmonary artery and the left side of the heart. All chambers ere of normal size ith large distance from the inner all to the external heart border. There were elongation and distortion of the right ventricular outflow tract and elev tion of the left pulmonary artery due to extrinsic pressure. I addition there as superior vena caval diverticulum, in hich dy remained at least 22 seconds after the right atrial injection.

An exploratory thoracotomy was performed on Sept. 29 1965. There ere small, clear yellow pleural effusions bilaterally. The pericardium as gray and rigid and no cardiac movement was visible. The pericardium stripped y easily from gray slightly hemorrhagic, gelatinous substance beneath. The gelatinous substance as adherent to the myocardium and it as impossible t determine the border between tumor and myocardium. The distance f om the pericardium to myocardium was about 7 to 8 cm. over the right side of the heart. Within this area there was, in addition, ca ity 4 cm in diameter hich as filled ith yellow brow fl id. A definitiv pericardiectomy as not attempted but as much of the tumor as possible was scooped out.

The tumor material (Fig. 9) consisted of broad sheets and nests of relatively small, uniform, spindle shaped cells. The nuclei ere oval and contained only modest amount of chromatin and single nucleolus. Mitoses ere present but ere not abundant. There ere no bizarre cells. The cyst in the tumor was lined with epithelioid cells hich resembled mesothelioma and had uclei similar to the remainder of the tumor. The epithelioid cells contained numerous periodic acid-Schiff stain (P. A. S.) positive granules. Similar granules ere present in smaller numbers throughout the tumor. The pathologic diagnosis as fibrous mesothelioma of the pericardium.

Postoperatively the patient received cobalt-60 radiation therapy to the heart for total tumor dose of 3,128 rads. This resulted in marked reduction in heart size and improved exercise tolerance. He as also treated with digoxin, prednisone, and testosterone. He felt better for some time in spite of eventual increase in heart size and spread of tumor into the right hemithorax.

I January 1966, he had an acute episode of left shoulder pain and shortness of breath. H was readmitted to UCLA in respiratory distress. He w found to ha an extensive tumor spread to both pleural cavities with pleural effusions. He soon lapsed into coma and died on Feb. 2, 1966.

An utopsy revealed intrathoracic dissemination of the tumor ith microscopic invasion of the myocardium, lung, diaphragm, and intercostal tissues. There were no extrathoracic metastases. Microscopic examination confirmed the diagnosis of fibrous mesothelioma of the pericardium.

Fig. 3. Right trial and right entricular tracings (Case 1). The ECG is of Lead I in both figures above.

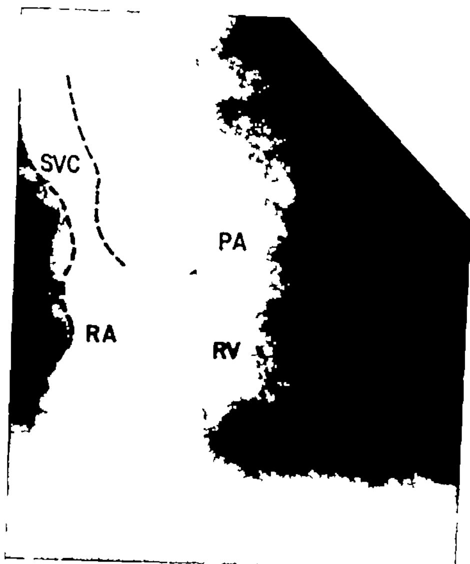


Fig. 4 Right angiocardiogram (Case 1) See text for description. The outer border of the right atrial pericardium is identified by black arrows. *PA* = pulmonary artery *RA* = right atrium, *RV* = right ventricle, and *SVC* = superior vena cava.

Discussion

The histories presented above are reminiscent of the cases previously reported Almost every patient has had chest pain which was intermittently pleuritic a cough which was usually dry and various manifestations of congestive heart failure Cervical veins were often but not invariably distended a pulsus paradoxus was present in approximately a third of the subjects and commonly there were signs of pleural effusion Palpation of the chest usually but not constantly disclosed a quiet precordium Heart sounds were often faint and there were often fleeting pericardial rubs

Chest x rays usually suggested pericardial effusion and ECG s showed nonspecific S-T segment and T wave changes consistent with pericarditis. Arrhythmias were unexpectedly uncommon in view of the fact that they are often present with metastatic myocardial[illegible] and pericardial[illegible] involvement. However there are several reports of heart block quoted in Dawe s review [1] and one patient reviewed was noted to have atrioventricular dissociation[7] all these subjects had invasion of the cardiac conduction system by mesothelioma. In three cases[illegible] there was right axis deviation which in two instances progressed rightward before death This is reminiscent of our first patient who had no intraventricular conduction defect and no gross anatomic reason for right axis deviation

In the cases described in the literature when pericardiocentesis was done no fluid



Fig. 5A Photomicrograph (×42) of tumor (Case 1) showing dense areas of the fibrous tissue with interspersed clefts. T the left and center there are more frequent epithelioid cells and multiple clefts lined by epithelioid cells. The area outlined t the bottom is show in Fig. 5B



Fig. 5B High-power (×500) photomicrograph of the boxed area from Fig. 5A showing a cleft in the midst of dense fibrous tissue.

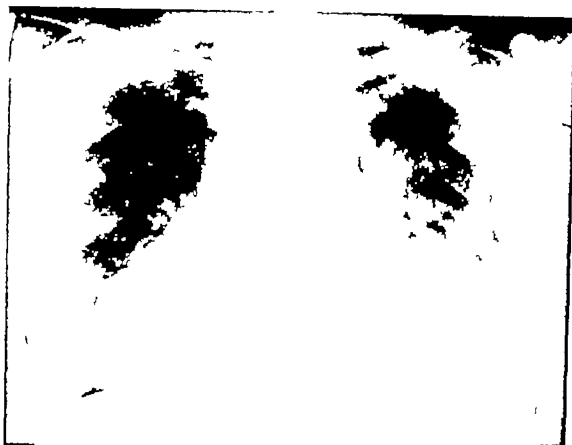


Fig 6A Posteroanterior roentgenogram (Case 2)



Fig 6B Cardiac blood pool scan (Case 2) showing a small intracardiac blood pool compared to the roentgenologic heart size There is wide separation between the heart (dark central area) and the lungs on both sides, as well as between the heart and the liver The light area surrounding the cardiac blood pool represents pericardial tumor

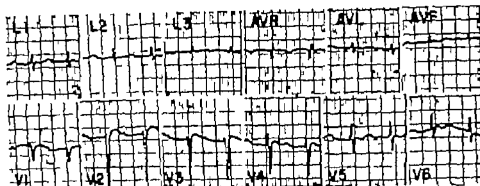


Fig. 7 ECG (Case 2).

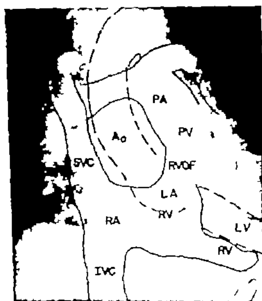


Fig. 8 Posteroanterior angiocardiogram following right atrial injection (Case 2). The left heart chambers have been sketched in, based on later films. All chambers are of normal size. There is suggestion of superior vena caval narrowing just below the right pulmonary artery. There is distortion and irregularity of the right ventricular outflow tract on its left side, and elevation of the left pulmonary artery. The extrinsic pericardial mass is easily visualized on both sides. The superior vena caval diverticulum is an incidental finding. A = aorta, IVC = inferior vena cava, LA = left atrium, LV = left ventricle, PA = pulmonary artery, PV = pulmonic valve, RA = right atrium, RV = right ventricle, $RVOF$ = right ventricular outflow tract.

was obtained or the fluid was bloody and contained large amounts of protein. In our first case no pericardiocentesis was attempted and in the second case there were many dry taps. When pericardial fluid has been studied for malignant cells the yield of diagnostic information has been poor. Intrapericardial air studies may be helpful when they can be done safely. Such a study may show an intrapericardial mass with a thin pericardium[26] or inability of the air to enter part of the pericardial cavity.

Angiography may show obstructive lesions in the systemic venous or pulmonary arterial system. On cineangiography the cardiac chambers in both cases reported here ended early diastole abruptly as is seen in constrictive pericarditis.[44]

In both our cases, as in those reported cases diagnosed during life, exploratory surgery and biopsy were required for definitive diagnosis.

In most cases at autopsy or surgery the heart is encased in tumor and the pericardium is extremely thick, often adhering to and invading the myocardium. There is a



Fig. 9. Photomicrograph (×125) of tumor (Case 2). There is a nest of epithelioid cells seen in the upper left hand corner. Below and to the right of that area are seen multiple clefts, some of which have been cut tangentially lying in a loose fibrous network.

high incidence of vena caval encirclement and narrowing.[1,4,7,13,14] The myocardium is variously invaded but the endocardium is usually spared. The right atrium may be invaded directly[1] or through the coronary sinus.[13] Atrioventricular block or dissociation may be produced by invasion of the conducting or pacemaker tissues.[1,13,24] Also the tumor may erode into a coronary artery and present as a myocardial infarction[1] or acute pericardial tamponade. The tumors usually spread locally into both hemithoraces and the mediastinum; rarely are there metastases outside the thorax.

Microscopically mesotheliomas are classified as epithelial, fibrous, or mixed epithelial and fibrous.[1] In the recent literature most cases have shown the mixed or fibrous pattern. Both of our cases were predominantly fibrous with many areas of clefts lined by epithelioid cells and other areas of round or oval cell clusters appearing similar to Dawe's own case.[1]

There is no association of pericardial mesothelioma with asbestosis in contradistinction to the high correlation of asbestosis with pleural and peritoneal meso thelioma.[8]

There is no specific or established therapy for primary pericardial mesothelioma which has a 60 per cent death rate within 6 months.[24] Radiation therapy may produce temporary improvement as it did in our Case 2.[4,23,27]

Summary

Two patients with primary pericardial mesothelioma are presented in detail and the world literature is reviewed. Both patients presented with chest pain and the symptoms and signs of congestive heart failure with a very high venous pressure. Only one had a pulsus paradoxus. Both had nonspecific ECG changes and cardiomegaly. Multiple pericardiocenteses were dry in one case. Cardiac catheterization demonstrated findings characteristic of restrictive cardiac disease. Both cardiac blood pool scans and angiocardiography demonstrated pericardial thickening. Definitive antemortem diagnosis required open pericardial exploration and biopsy. No specific therapy exists for this condition.

We wish to thank Drs. Albert Kattus, Jr., Kenneth Clay, and Gordon Frank, for allowing the inclusion of Case 1 in this report.

REFERENCES

1. Da e C. J Wood D A., and Mitchell, S. Diffuse fibrous mesothelioma of the pericardium, Cancer 6 794 1953.
2. Goodwin, M C. Diff se mesothelioma, Cancer 10:298 1957
3. Sarrell, W G. Primary pericardial me othelioma, Amer. He rt J 19:310, 1955
4. Waldhausen, J A., Lombardo, C. R. and Mor row A. G. Pulmonic stenosis due t compression of the pulmonary artery by an intrapericardial tumor J Thorac. Cardiovasc. Surg 37:679 1959
5. Thomas, J and Phythyon, J A. Primary mesothelioma of the pericardi m, Circulation 15:385 1957
6. Forest, J L and Koroels, M C. Primary mesothelioma of the pericardium, Amer J Cardiol. 5 126, 1960.
7. Sherry S., and Lacy P Clinical pathologic conference. Pericardial disease with effusion, systemic invol ement and pulmonary edema, Amer J Med. 33:447 1962.
8. Burr R. E. Primary mesothelioma of the pericardium, Amer J D Child. 108:98, 1964
9. Berkman, N M Rare tumors in children, Amer J Roentgen. 93:67 1965
10. Norman, M G Primary mesothelioma of the pericardium, Canad. Med. Ass. J 92 129 1965.
11. Cardoso, E. L., and Saltet, J F A case of mesothelioma pericardn, Acta Med. Scand. 178:301 1965
12. Chaves, E Primary malignant mesothelioma of the pericardium, Dis Chest 57:663 1965
13. Pietra, G. G., Silber E., Levine, B nd Pick, A. Clinical pathologic conference Malignant mesothelioma of the pericardium, Amer. Heart J 78:545 1968.
14. Arnola, L Cerasoino, R., Ferrari, A et al Primary pericardial mesothelioma, Acta Car diol (Brux) 15:281 1960
15. DeChenay C Mesothelioma of the pericar dium, Texas Rep Biol. Med 18:395 1960
16. Bjernulf A Bjork, L and Cullhed, I Pericardial mesothelioma presented as constrictive pericardial disease Scand J Thorac Cardiovasc Surg 22:227 1968
17. De Cristo, K A nd Hamblin, R. J Primary malignant mesothelioma of the pericardium, Calif Med 107 175 1967
18. Van de W ter J M and Allen, W H Pericardial mesothelioma, Ann Thorac Surg. 3 162 1967
19. Dooley B N Beckmann C nd Hood, R H J Primary mesothelioma of he pericardium. Successf l surgical removal, J Thorac Cardiovasc Surg 55 719 1968.
20. Foxon, R L Seam D E and Lester R G Intrapericardial mesothelioma I teresting radiology findings on pneumopericardium. Report of ase, Dis Chest 51:554, 1967
21. Li thicum, C. M. Localized mesothelioma of the pericardium, Southern Med. J 62:207 1969
22. Hureau, J Robin C. L. and Kerners, J P. Et de anatomo-clinique d' mesothelioma mali du pericarde essai de traitement medical Arch. Mal Coeur 52:522, 1959
23. Stutsonaskaia, A. L., and Iudin, I G. A case of mesothelioma of the pericardium in early childhood Probl. Oncol. 4:637 1958.
24. Murot A. Contribution à l' tude des tumeurs primitives d pericarde. Thèse présenté à la faculté Mixte Medicine et de Pharmacie de Lyon, Dec. 16, 1960, Macon.
25. Gonin, A Perola, A., Delahaye, J I et al. Primary malignant tumors of the pericardium, Arch. Mal. Coeur 55 129 1962.
26. Galil-Ogly G. A., and Poroshin, K. K. Pericardial mesothelioma, Arkh P t. 28 72, 1966.
27. Kobylinski, S. Primary mesothelioma of the pericardium, Zbl. Allg. P th. 111 113, 1968.
28. Karpel, G. G. Mesothelioma of the pericardium with metastases, Arkh. P t. 27 72, 1965.
29. Lotto, A., Capelli, F and Coggi, G. Clinical and natomopathological observations on a case of primary mesothelioma of the pericar dium, Atti Accad. Med. Lombard. 21:274 1966.
30. Van Valderen, W and Van de Wez, R. A: A case of mesothelioma of the pericardium, Nederl. T Geneesk. 113:200, 1969
31. Piwnica, A., Soyer R., and Goux, J F Primary mesothelioma of the pericardium. A propos of tw cases, J Chir (Paris) 95 357 1968.
32. Kumagai, K., Sato, T and Tamura, H. Clinicopathologic conference No. 200. Case of malignant mesothelioma of the pericardium, Iryo 23 101 1969
33. Mahaim, L.. Les tumeurs et les polypes du coeur Paris, 1945, Masson & Cie, p. 129
34. Kauffman, S. L., and Stout, A. P Mesothelioma in children, Cancer 17:539 1964.
35. Shelburne, S. A. Primary tumors of the heart Ann. Intern. Med. 9:340, 1935.
36. E erougham, S. Primary endothelioma of the pericardium. Report of case, Surg. Clin. N Amer 11:975 1931.
37. Andolf N Bergmark, G., and Gellerstedt, N U cas de coelothelioma epicordis, Acta Soc. Med. Upsal. 42:363, 1937
38. Harvey W P Clinical aspects of cardiac tumors, Amer J Cardiol. 21:328, 1968.
39. Goodwin, J F The spectrum of cardiac tumors, Amer J Cardiol. 21:307 1968.
40. Deuleta, D T Grollman, J H and MacAlpin, R. N Cineangiocardiographic demonstration of the diastolic snap i constrictive pericarditis, Radiology 86 1056 1966.
41. Selikoff I J Churg, J and Hammond E. C.: Relation between exposure to asbestos and mesothelioma, New Eng. J Med. 272:560 1965.

Mass indices of the ventricles at autopsy in children

*Horacio J. A. Rimoldi, M.D., Ph.D.**
*Rosalia E. A. Parma, Ph.D.***
*Patrick C. McAuley, Ph.D.**
*Maurice Lev, M.D.****
Chicago, Ill.

The weights of the right and left ventricles and the ratio of these weights represent important morphologic data at autopsy. An index of these weights may be obtained from the weights of the parietal walls of the ventricles. The assumption is thereby made that the septum is proportionately divided into the right and left ventricles in most hearts. To obtain the weights of the parietal walls it is necessary to cut the heart into fragments. This destroys the specimen for further teaching purposes or correlation with clinical data.

We have devised a method which we believe gives a good index at autopsy of the weights of the right and left ventricles and the ratio of these weights, in children from 3 months to 15 years of age, without cutting the heart into fragments.

Materials and methods

In previous work[1,2] we studied 21 modalities of the normal child's heart from birth to 15 years of age, using age, weight, and height of the child as points of reference. These modalities included thickness of parietal walls at various points, various parameters indicating sizes of chambers, weight of the entire heart, weight of the parietal walls of the atria and ventricles, and sizes of atrioventricular and semilunar orifices.[1] We also devised a method for predicting what the values of these modalities would be for a normal child of a certain age, weight, and height.[1] We then developed the concepts of normality, probable normality, abnormality, and probable abnormality in judging a modality in an unknown heart.[3] The above work led to the development of a method of making statements as to the above modalities in a group of congenitally abnormal hearts belonging to a single entity.[4,5] The present work is an extension of this problem whereby modalities previously used are employed to create a mass index of the right and left ventricles and their ratio in the normal child's heart. The purpose of these indices is to be able to make statements of a tendency toward absolute and

From the Congenital Heart Disease Research and Training Center, Hektoen Institute for Medical Research; The Departments of Pathology of Northwestern University Medical School, The University of Chicago School of Medicine, and the University of Illinois College of Medicine; and the Loyola Psychometric Laboratory, Loyola University, Chicago, Ill.

This investigation was supported in full by Grant HE 07605-06 from the National Heart Institute, National Institutes of Health, Bethesda, Md.

Received for publication July 24, 1970.

Reprint requests to: Maurice Lev, M.D., 637 S. Wood St., Chicago, Ill. 60612.

*Now at the University of Buenos Aires.

**Now at the Medical College of Ohio at Toledo, Ohio.

***Career Investigator and Educator, Chicago Heart Association.

relative hypertrophy of the right and left ventricles in a group of congenitally abnormal hearts belonging to a certain entity

The volume of the mass of muscle multiplied by the specific gravity gives the weight of the muscle. If we were to lay open each chamber always in the same manner forming thereby an irregular mass of muscle of relatively constant form, then the inner area multiplied by the thickness would give the volume of the muscle mass. Since we cannot obtain the inner area directly we can obtain an index of this area by taking certain constant measurements in two planes of the inner surface of the heart roughly perpendicular to each other Thus, in the case of the right ventricle we may use the length of the inlet and the partial perimeter of the inlet, and the length of the outlet and the perimeter of the outlet, and multiply these by the thickness of the wall in these areas to obtain an index of the volume of the mass of muscle. In the case of the left ventricle we may average the length of the inlet and outlet, and multiply these by the perimeter of the left ventricle and by the maximum thickness of the wall to again obtain an index of the volume of the mass of muscle.

Mass indices of the right and left ventricles Thus mass indices of the right and left ventricles were estimated as follows

$$\text{Mass index of } RV\ (MI_{RV}) = (TA)\ (P\ RV_i)\ (RV\ T) + (PA)\ (P\ RV_o)\ (RV\ P) \quad (1)$$

$$\text{Mass index of } LV\ (MI_{LV}) = \frac{(MA + AA)}{2}\ (P\ LV)\ (LV\ M) \quad (2)$$

Where

TA = length from the tricuspid ring to apex (inflow right ventricle) in centimeters,

$P\ RV_i$ = perimeter of right ventricle (inlet) in centimeters,

$RV\ T$ = thickness of wall of right ventricle in the tricuspid region in centimeters,

PA = length from the pulmonic ring to apex (outflow right ventricle) in centimeters,

$P\ RV_o$ = perimeter of right ventricle (outlet) in centimeters,

$RV\ P$ = thickness of wall of right ventricle in the pulmonic region in centimeters,

MA = length from mitral ring to apex (inflow left ventricle) in centimeters,

AA = length from aortic ring to apex (outflow left ventricle) in centimeters,

$P\ LV$ = perimeter of left ventricle in centimeters,

$LV\ M$ = maximum thickness of wall of left ventricle in centimeters.

The method of taking these measurements has been previously discussed,[1,7] and is recapitulated in Table I

In formula (1) the first term is an index of the volume of the mass of the walls for the inflow section of the right ventricle. The second term is an index of the volume of the mass of the walls of the outflow tract of the same ventricle. Similarly formula (2) is an index of the volume of the walls of the left ventricle.

Both indices were computed for 82 *normal* subjects. As the specific gravity of the myocardium does not vary appreciably in normal hearts, the mass indices of the right and left ventricles were compared with the weights of the parietal walls of the right (RV) and left (LV) ventricles, respectively In Figs. 1 and 2 the actual weights RV and LV of 36 out of the 82* subjects were plotted against their respective mass indices. Validity of the indices is supported by the linear relationship found in both cases. The correlation between the actual weight RV and mass index of RV had a value of 0 961 with a standard error of estimate of 1.847 The correlation between the actual weight LV and the mass index of LV was 0.980 with a standard error of estimate of 2 923

Having thus given information concerning the validity of the indices, we studied their relationship with age, weight, and height of the individuals. Several curve-fitting procedures were used, but none gave a satisfactory fit. Instead, it became apparent that the data should be split into two subsamples one including all cases up to 1 019 years of age after conception—that is, about 14 weeks after birth (Sub-

*Only 36 cases could be used because sizable fragments of muscle had been removed by the prosector in the remaining cases.

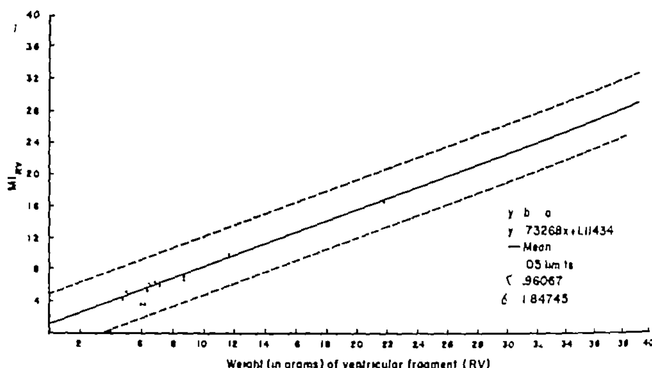


Fig 1 Graphic representation of the relation between the weight of the parietal wall of the right ventricle (RV) and the mass index of the right ventricle (MI_{RV})

Table I *Method of taking measurements*[1,7]

TA	= Taken from a point at the tricuspid annulus in the center of the posterior wall to the apex
PRV	= Taken in a plane midway between apex and tricuspid annulus over the inferior and septal walls up to the lower margin of the septal band and over the anterior wall up to the level of attachment of the anterolateral papillary muscle
RV T	= Thickness of the right ventricle without t beculae 0 5 to 1 0 cm. distal to the tricuspid orifice
PA	= Taken from a poi t of the middle of the septal cusp of the pulmonic valve to the apex
PRV	= Taken in a plane pa allel to the pulmonic valve, and passing through the lower margin of the arch of the crista over the pariet l nd septal band surf ce
RV P	= Entire thickness of the right ventricle 0 5 to 1 0 cm below the pulmonic orifice
MA	= Taken from a point on the mi tral n ulus at the center of the inferior wall to the apex
AA	= Taken from the base of the right aortic cusp to the apex
P LV	= Taken in a plane roughly parallel to the mitr l and aortic orifices midway between the apex and these orifices
LV M	= Maximum thickness of the left ventricle without trabeculae

sample A)—and the other comprising the older subjects (Subsample B) A similar phenomenon was observed in relation to body weight in which case the cutting point corresponded to 4 750 Kg and in relation to body length the cutting point being 59 cm Subsample A comprised 27 cases and Subsample B 55 cases.

The relation between age body weight and body length (independent variables) and the mass index of each chamber were studied separately in both subsamples.

SUBSAMPLE A As concerns the relationship of the mass index of the right ventricle (MI_{RV}) with age no function could be derived from these data and hence no statement can be made concerning the changes in MI_{RV} with age below 3 months. With reference to the mass index of the left ventricle (MI_{LV}) the relationship is shown in Fig 3 The line of best fit can be expressed by the simple linear equation

$$y = bx + a \quad (3)$$

where $y = MI_{LV}$ x represents age measured

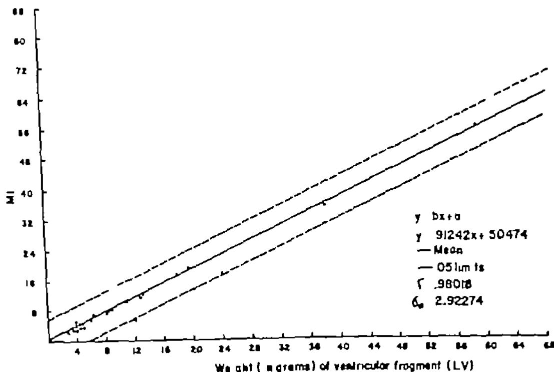


Fig. 2. Graphic representation of the relation between the weight of the parietal wall of the left ventricle (LV) and the mass index of the left ventricle (MI).

from the moment of conception. b indicates the slope of the line of best fit, and a represents the intercept.

The correlation between age and MI_{LV} had a value of 0.722 with a standard error of estimate of 1.006. This correlation is significant at the 1 per cent level.

The equation to predict MI in terms of age is

$$MI = 17.315 \text{ age} + (-9.193) \qquad (4)$$

As to the relationship between the mass index of each chamber and body weight and body length no mathematical function giving a satisfactory fit could be determined.

SUBSAMPLE B. In Subsample B it was found that the relationship between each of the independent variables—age (Figs. 4 and 5), body weight, and body length—and MI and MI_{LV} could be better represented by using the formula

$$y = ax^b \qquad (5)$$

or when expressed in linear form

$$\log y = b \log x + \log \qquad (6)$$

where y represents either MI_{RV} or MI_{LV}. x can be either age or body weight or body length. b is the slope of the line of best fit, and the logarithm of a represents the intercept. Formula (6) indicates that the line of best fit for the dependent variables MI_{RV} and MI_{LV} is obtained when the logarithms of age, body weight, and body length are used. As was indicated before age should be considered not from the moment of birth but from the moment of conception. This means that in order to use formula (6) the logarithm of the actual body weight (measured in kilograms) and the logarithm of the actual body length (measured in centimeters) should be used. When age (measured in years) is the independent variable, however, nine months, i.e. 0.75 year should be added to it and then the logarithm of the total value should be inserted in the formula.

Tables II and III present the values of the constants to be used for predicting MI_{RV} and MI_{LV} in normal hearts, respectively. The correlation index (r), the standard error of estimate (e_s) and the

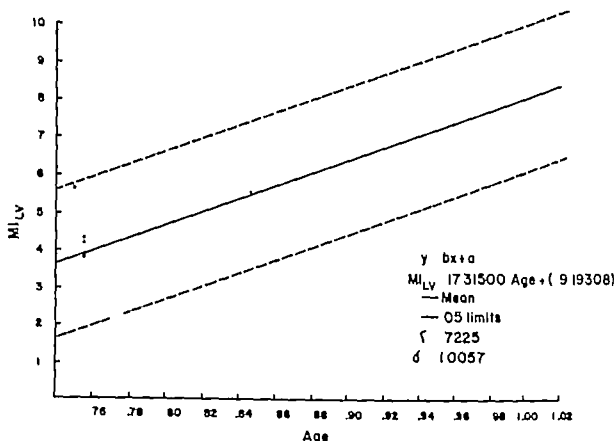


Fig 3 Graphic representation of the relation between age and the mass index of the left ventricle (MI_{L}) in children under 1 02 years of age.

number of cases (N) used to determine these values are indicated below each equation * In both tables the equations have been listed in decreasing order of predictive efficiency as evidenced by the value of the correlation indices.

It should be noticed that in formula (6) the dependent variable y is given in logarithmic units. Consequently once any of the equations in Tables II or III has been used it is necessary to find the antilogarithm of the result in order to express the predicted value of the respective mass-index in terms of the original unit of measurement.

The examination of the curves (Figs. 4 and 5) and the high values of the correlation indices are an indication that the prediction that can be made about the magnitude of the mass indices using age body weight, or body length will be satisfactory after the transition period Nevertheless, the possibility of improving this prediction by using any combination of the three independent variables was considered advisable

For this purpose stepwise multiple correlations between each mass index and the three or any two independent variables were computed By this method the independent variables were introduced into the analysis in descending order of importance as to the additional reduction contributed by each of them in the variability of the dependent variable in question The relative importance of the independent variables included in each multiple linear regression was measured by appropriate F tests.[9]

Regarding MI_{RV} it was found that the only case in which there was a significant improvement of the prediction was when age was added after using weight ($P < 0.05$) The formulas for prediction multiple correlation coefficient ($R_{MI_{RV}} \cdot w_A$) standard error of estimate (σ) and number of cases (N) are given in Table II

As to MI_{LV} it was found that use of multiple regressions did not improve the prediction significantly

*The is given in logarithm units, since logarithms were used all the way through in the computations.

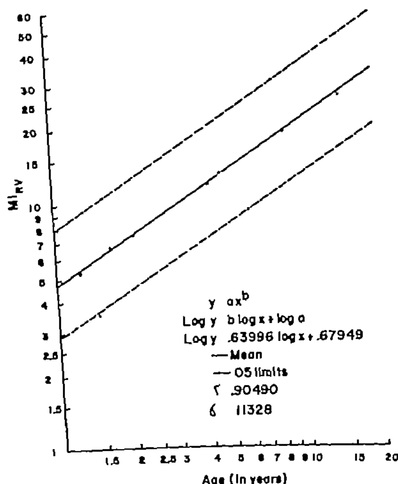


Fig. 4 Graphic representation of the relation between age and the mass index of the right ventricle (MI_{RV}) in children older than 1.0192 years after conception.

Mass ratio Formulas (1) and (2) provide mass indices of the walls of both ventricles. Since we are assuming that the density of the heart muscle is constant throughout, then the ratio of (1) over (2) may be considered as an index of mass ratio This will be called index RV/LV The actual ratio of the weights of the right and left ventricles will be called RV/LV Then

$$\text{Index } RV/LV = \frac{(TA)\,(P\ RV)\,(RV\ T) + (PA)}{\frac{(MA + AA)}{2}\quad (P\text{-}LV)}$$

$$\frac{(P\ RV)\,(RV\ P)}{(LV\ M)} \qquad (7)$$

The index RV/LV was computed for the 82 normal subjects in the sample. Graphs corresponding to plotting index RV/LV against age (Fig 6) body weight, and body length were made. The graphs for body weight and body length were similar to that for age. The validity of the index RV/LV is supported by comparing Fig 6 with curve No 94 in Rowlatt, Rimoldi, and Lev[1] which shows the relationship between age and RV/LV

As was the case with the mass indices of both ventricles, the study of the curve in Fig 6 showed the necessity of splitting the sample into Subsamples A and B

SUBSAMPLE A We have been unable to find a function that will fit the index RV/LV below the age of 1.019 years as related to age, weight, or height.

SUBSAMPLE B. In Subsample B the average value of index RV/LV was 0.548 with

Table II Formulas for predicting MI_{RV} in terms of age (A) body weight (W) and body length (L) and corresponding correlation index standard error of estimate (σ) and number of subjects (N) for patients aged between 3 months and 15 years

	Equation	σ	N
a	$\text{Log } MI_{RV} = 0.51653 \log W + 0.26582 \log A + 0.28616$; $^*MI_{RV}$ W A = 0.929	0.104	47
b	$\text{Log } MI_{RV} = 0.83851 \log W + 0.06297$; $r = 0.919$	0.10741	47
c	$\text{Log } MI_{RV} = 0.63966 \log A + 0.67949$; $r = 0.905$	0.11328	55
d	$\text{Log } MI_{RV} = 1.81141 \log L + (-2.59912)$; $r = 0.890$	0.12124	55

*Since data on body weight of eight subjects in subsample B were not available, only 47 patients were used to determine equations a and b

Table III Formulas for predicting MI_{LV} in terms of age (A) body weight (W) and body length (L) and corresponding correlation index standard error of estimate (σ) and number of subjects (N) for patients aged between 3 months and 15 years

	Equation	σ	N
a	$\text{Log } MI_{LV} = 0.92178 \log W + 0.23745$; $r = 0.943$	0.097	47
b	$\text{Log } MI_{LV} = 2.04140 \log L + (-2.72240)$; $r = 0.903$	0.125	55
c	$\text{Log } MI_{LV} = 0.69537 \log A + 0.92019$; $r = 0.900$	0.127	55

*Since data on body weight of eight subjects in subsample B were not available, only 47 patients were used to determine equations

a standard deviation of 0.128 It was found that it could be interpreted as a constant in all cases.

Method of using the mass-indices and their ratio

We have developed indices of mass of the right and left ventricles and their ratio in children from 3 months to 15 years of age which can be derived from certain simple measurements in the heart We have studied these indices in a sample of normal hearts correlating the actual value of the indices with age weight, and length of the individual From this correlation study we developed various mathematical equations which allow us to predict what the indices are in the heart of a normal individual of a certain age weight and height.

In an abnormal heart similar measurements will yield values of indices different from those of the normal heart. Given an individual of certain age weight and height we may therefore compute the indices from the actual measurements and also compute the indices from our equations were the heart to be normal Comparison of both values the actual and the predicted will enable us to make statements as to the normality or abnormality of the actual indices.

Thus in each individual heart measurements of various modalities mentioned in equations (1) and (2) are made From this, the actual values of MI_{RV} and MI_{LV} and index RV/LV are computed from equations (1) (2) and (7) We now calculate the predicted normal value for the indices. The normal value of the index RV/LV is considered a constant 0.548 The predicted normal values for MI_{RV} and MI_{LV} are computed by using equations as given in Tables II and III respectively If age alone is known equations c and c' should be used if only body weight equations b and a if only body length equations d and b Or if any combination of independent variables is known selection of the appropriate regression equations should be made according to the order in which they are presented in Tables II and III Thus, if age weight and length or only age and

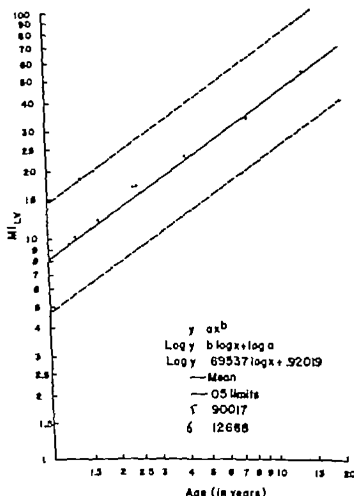


Fig. 5 Graphic representation of the relation between age and the mass index of the left ventricle (MI_{LV}) in children older than 1.0192 years after conception.

weight are known equations a and a should be used If age and body length equations c and b if weight and length equations b and a

At this point we know the actual value and the predicted normal value of the indices. We now compare both values in order to determine how far the actual value deviates from the predicted normal one if any

$$\frac{\text{Actual value} - \text{Predicted value}}{\text{Standard error of estimate}} = \text{Normal deviate (i.e., number of sigmas the actual value deviates from the predicted normal one).} \quad (6)$$

It should be noted that for Subsample B the standard error of estimate and the predicted value of the indices obtained by using any of the equations in Tables II and III are expressed in logarithmic units. Hence, in order to perform the comparison indicated in formula (6) the logarithm of the actual value should be used. In the case of MI_{LV} for cases below the age of 3 months, the original unit of measurement is used as indicated by the linear function in formulas (3) and (4)

If the deviation from the predicted normal value is within $\pm 0.6745\ \sigma$ the actual value is considered to be normal If the deviation is $\pm 1.960\ \sigma$ or more, it is considered to be abnormal If the deviation falls between $\pm$ (0.6745 to 1.10) σ it is considered to be probably normal If it falls between $\pm$ (1.10 to 1.96) σ the actual value is considered to be probably abnormal.

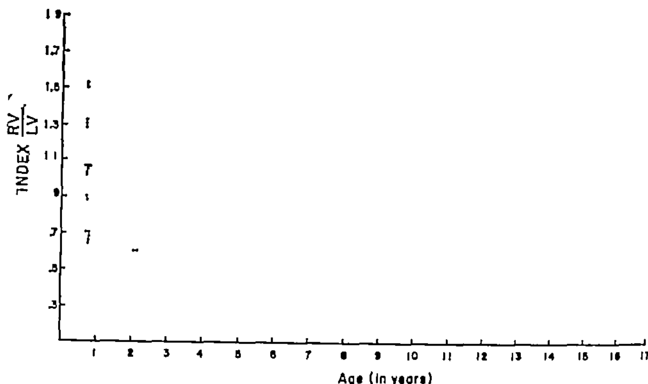


Fig 6 Graphic representation of the relation between age and index RV/LV in children.

We have now categorized the actual value of the indices in each particular heart as being either normal probably normal abnormal or probably abnormal We now plot in a bar graph the proportion of cases falling into each category From this graph we make a statement that there is a *tendency* for the various indices to be normal increased or decreased From the composite picture of the indices, together with the actual weights of the whole hearts, in the individual entity under scrutiny statements can now be made of *tendencies* toward relative or absolute hypertrophy or atrophy of both ventricles (Table IV)

Discussion

The hearts used in this study had previously been opened then fixed in 4 per cent formaldehyde (10 per cent formalin) for varying periods of time We had previously found that measurements do not vary perceptibly after a heart has been opened and fixed for 72 hours. All the hearts used were considered to be normal since there was no evidence of hypertension in the greater or lesser circulation or wasting disease in any case. Measurements were made with a flexible ruler

It must be emphasized that the methodology we have used in the past for equating sizes of chambers, thickness of walls, and sizes of orifices[2,8] and that we now propose for equating muscle mass, pertain to groups of congenitally abnormal hearts belonging to a certain entity in children up to 15 years of age They are not used to make definitive statements about an individual heart This is due to the fact that the sample of normal hearts used for comparison with abnormal hearts was small and the variation in this sample was too great to permit meaningful statements to be made about an individual heart in question unless the values in the individual heart fell into the categories of (1) frankly normal or (2) frankly abnormal However when dealing with a group of hearts belonging to a single entity and with the concepts of normality probable normality abnormality and probable abnormality meaningful statements can be made about a tendency toward increase or decrease in a certain modality

As shown above we have been unable to derive a mass index for RV and an index RV/LV in the transition period (below the age of 3 months) It is a question whether the mass index of LV evolved in this age group by itself will prove useful

The question arises as to whether the mass index should be modified by the

Table IV Method of making a diagnosis of hypertrophy or atrophy of ventricles

Weight of heart	*MI*	*MI*	*Index* $\frac{RV}{LV}$	*Diagnosis*
+	+	N	+	Right ventricular hypertrophy
+	N	+	−	Left ventricular hypertrophy
+	+	+	N	Relatively proportional biventricular hypertrophy
+	+	+	+	Bilateral ventricular hypertrophy with dominant right ventricular hypertrophy
+	+	+	−	Bilateral ventricular hypertrophy with dominant left ventricular hypertrophy
+N−	+	−	+	Hypertrophy of the right ventricle with atrophy of the left ventricle
+N−	−	+	−	Hypertrophy of the left ventricle with atrophy of the right ventricle
−	−	−	N	Proportionate atrophy of both ventricles
−	−	−	−	Atrophy of both chambers with dominant atrophy of the right
−	−	−	+	Atrophy of both chambers with dominant atrophy of the left

specific gravity. The specific gravity of normal myocardium, either fresh or fixed, does not differ appreciably with age, and the difference between that of the right and left ventricles is minimal. Masshoff, Scheidt, and Reimers[8] found the specific gravity of the heart muscle below the age of 1½ years to be 1.047 and above that age to be 1.055. This does not have an appreciable influence on the weight. Hence, our mass indices in the normal heart can disregard the specific gravity. It is not known, however, whether the specific gravity differs appreciably in diseased states. Since the purpose of the mass indices is to evaluate abnormal hearts, if the specific gravity should be found to be sufficiently variable in the latter, then our mass indices will have to be corrected by the specific gravity.

Summary

Mass indices of the right and left ventricles in children were computed by obtaining an index of the volume of the mass of muscle. These indices compared favorably to the actual weights of the parietal walls of the right and left ventricles. The indices were then studied in 82 normal children using age, weight, and height as independent variables. It was found necessary to separate the indices from birth to three months of age from those of subjects older than three months. Below three months of age, no relationship could be found between the mass index of the right ventricle, but a relationship was present between that of the left ventricle and the independent variables. Above three months of age, there was a relationship of both mass indices to the independent variables. The mass index RV/LV was then studied in the above two age groups. Below the age of three months no relationship could be found with the independent variables. Above three months of age, the mass ratio was found to be a constant. These data may be used to evaluate a group of malformed hearts belonging to a single entity in congenital heart disease.

REFERENCES

1. Rowlatt, U. F., Rimoldi, H. J. A., and Lev, M.: The quantitative anatomy of the normal child's heart, Pediat. Clin. N. Amer. 10:499, 1963.
2. Rimoldi, H. J. A., and Lev, M.: A note on the concept of normality and abnormality in quantitation of pathologic findings in congenital heart disease, Pediat. Clin. N. Amer. 10:589, 1963.
3. Lev, M., Rimoldi, H. J. A., and Rowlatt, U. F.: The quantitative anatomy of cyanotic tetralogy of Fallot, Circulation 30:531, 1964.
4. Lev, M., Rimoldi, H. J. A., Eckner, F. A. O., Melhuish, B. P., Meng, C. C. L., and Paul, M. H.: The Taussig-Bing heart: qualitative and quantitative anatomy, Arch. Path. 81:24, 1966.
5. Lev, M., Rimoldi, H. J. A., Paiva, R., and Arcilla, R. A.: The quantitative anatomy of simple complete transposition, Amer. J. Cardiol. 23:409, 1969.
6. Lev, M., Joseph, R. H., Rimoldi, H. J. A., Paiva,

R. and Arcilla, R. A. The quantitative anatomy of isolated ventricular septal defect Amer. Heart J 81:315 1971
7 Lev M Rowlatt U F and Rimoldi H J A. Pathologic method for study of congenitally malformed hearts Method for electrocardiographic and physiologic correlation Arch Path. 72:493 1961
8 Mitzhoff W Schmidt, D and Reiners, H. F Quantitative Bestimmung des Fett-und Myocardgewebes im Leichenherzen, Virchow Arch. (Path Anat.) 312:184 1967
9 Fryer H C. Concepts and methods of experimental statistics Boston 1966 Allyn and Bacon Inc

Experimental and laboratory reports

Absence of Bowditch phenomenon in the ventricular muscle of hamsters with hereditary cardiomyopathy

Stephen Hajdu
Christian J. Posner
Bethesda, Md.

The contractility of most mammalian cardiac muscle in vitro is the result of two independent phenomena. Their contribution to the overall contractility, however, varies according to the frequency of stimulation. While in the middle frequency range the generation of contractions is shared by both phenomena, at high frequencies it is furnished almost entirely by the Bowditch phenomenon (BP) and at low frequencies by the Woodworth phenomenon (WP). Since the heart rate in vivo is in the range of stimulation called "high frequency" under in vitro conditions, the importance of the BP in support of life is overwhelming.

When it was reported[1] that a strain of hamsters spontaneously developed primary cardiac failure as a result of hereditary factors, an opportunity was presented to study the effect of the disease on these phenomena, for the hamsters have hearts small enough for in vitro studies and exhibit both phenomena. It was thought that if, as the result of the disease, both phenomena are equally depressed, it would have to be concluded that the defect in the contractile system is the common cause of the depression, since it would be highly unlikely that the disease would affect two independent functions equally (BP and WP). On the other hand, if the disease is restricted to only one of the phenomena, leaving the other intact, this would indicate a normal contractile system with the point of attack on the specific mechanism serving only this phenomenon. The present report demonstrates that the disease is restricted to the mechanism responsible for the BP in a manner that explains the primary weakness of the heart muscle.

Methods

The hamsters used in these experiments were divided into three groups. Group 1 consisted of seven healthy golden hamsters (NIH strain) with a body weight of 101 ± 14 grams and a wet weight of both ventricles of 216 ± 27 mg. Group 2 consisted of five hamsters with cardiomyopathy (BIO 82.62) without symptoms of cardiac failure. The average age was 88 ± 6 days, body weight, 84 ± 12 grams, and ventricular weight, 219 ± 48 mg. Group 3 consisted of seven animals with cardiomyopathy (BIO 14.6) and with severe congestive heart failure. The average age was 327 ± 14 days, body weight, 111 ± 9 grams, and ventricular weight 428 ± 82 mg. Since the animals in Groups 1 and 2 were considerably younger than those in Group 3, an additional group of ten healthy golden hamsters whose age range was 270 to 420 days, body weight 135 ± 18 grams, and ventricular

From the National Heart & Lung Institute, Laboratory of Kidney and Electrolyte Metabolism, Section on Experimental Cardiovascular Diseases, Bethesda, Md.
Received for publication July 4, 1970.

weight 135 ± 18 mg was later added to serve as appropriate age controls for the BIO 14 6 hamsters with severe congestive heart failure The weight of the ventricles given above does not include the weight of the triangular shaped muscle strip used for the measurement of tension Since the body and heart weights exhibited some variation among the different groups of animals and in order to obtain comparable values in the measurements of contractile tension strips of about the same size and shape were dissected from the right ventricular wall The average dimensions (width at the base × stretched length in millimeters) were as follows 5 6 × 11 7 for the NIH strain 6 5 × 11 8 for BIO 82 62* 5 4 × 15 1 for BIO 14 6 and 5 5 × 15 0 for the age control animals.

The animals were killed by exsanguination the chest was opened and a triangular shaped strip of muscle was excised from the free wall of the right ventricle beginning at the pulmonary artery The muscles were suspended in a lucite bath by attaching the pulmonary artery by means of a thin (26 gauge) stainless steel tubing to a Statham transducer (G7A-0 15 350) The narrow base of the muscles was tied to a lucite bar firmly attached through rack and pinions to the transducer One electrode was attached to the base of the muscle the other to the pulmonary artery Ringer Krebs solution[3] was used throughout the experiment vigorously gassed with a mixture of 95 per cent oxygen and 5 per cent carbon dioxide The temperature of the bath was kept between 21 and 22° C in order to avoid spontaneous rhythmicity which usually occurs above 23° C The transducer was coupled through a Brush Electronics (Model BL-520) amplifier to a Brush (B2902A) oscillograph A Grass (Model S4) stimulator was used with a SIU4 stimulus-isolation unit at intervals longer than 10 seconds the stimulator was controlled by an external time clock.

Results

The over-all state of contractility of the cardiac muscle is best studied by measuring isometric tension over the widest possible frequency range for the contribution of the two basic constituents of contractility (BP and WP) varies widely with the frequency of stimulation Fig 1 shows the tension at various frequencies (expressed as interval between stimuli) in three groups of hamsters Group 1 normal golden hamsters (NIH strain) Group 2 young hamsters with cardiomyopathy (BIO 82 6?) prior to the development of cardiac failure and Group 3 hamsters with cardiomyopathy (BIO 14 6) in the final stages of congestive heart failure. The interval tension curves of Groups 1 and 2 are similar They show the characteristic curve of a species endowed with both the BP and WP demonstrated by the rising tension at both ends of the curve. The wide separation of the two phenomena leaves the middle frequencies with scarcely any contractile tension This is in contrast to rat cardiac muscle in which the tension in the middle frequency range is only slightly depressed due to a considerable overlap of the two phenomena.[1] The interval tension curve of the diseased hamster heart (Fig 1 *BIO 14 6*) shows a parallel course with the curves obtained from the two control groups but only over the range of the WP (2 to 60 second interval) During the stimulus interval when the BP begins to develop in the normal animals (2 seconds and less) the curve of the diseased animals continues to decline, as though the BP were missing in these hearts. The interval tension curve of those animals serving as age controls for the BIO 14 6 group (see methods) is parallel to that of Groups 1 and 2 with an average tension of 1 8 gram at 0 5 second and 0 4 gram at 2 second intervals, demonstrating that the BP is present in the old healthy hamsters and that the absence of BP in the diseased animals is not due to their advanced age

In order to determine whether the BP is absent in the diseased hearts, all three groups of animal hearts were treated with ryanodine It has been shown that this drug irreversibly destroys the WP but leaves the contractility produced by the BP intact [1] In essence contractility remaining after treatment with ryanodine can be regarded as the result of BP alone. All hearts of the three

*Animals of the BIO 82.62 strain are supplied by the Trenton Experimental Laboratory Animal Company Bar Harbor, Maine 04609.

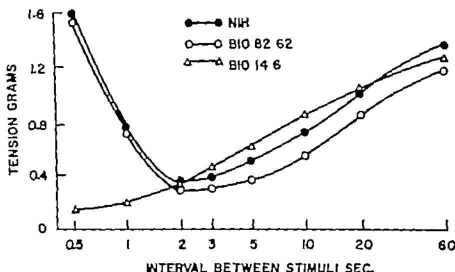


Fig. 1 Interval-tension relationship of the right ventricles of normal hamsters (*VIH* strain), hamsters with cardiomyopathy without cardiac failure (*BIO 82.62*) and those with cardiac failure in the terminal stage (*BIO 14.6*). Each point represents the average of 5 measurements on 5 different muscles.

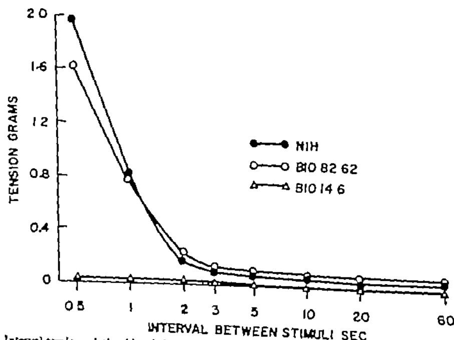


Fig. 2 Interval-tension relationship of the right ventricles of normal hamsters (*VIH* strain), hamsters with cardiomyopathy without cardiac failure (*BIO 82.62*), and hamsters with cardiac failure (*BIO 14.6*) after treatment with 0.05 mcg. per milliliter of ryanodine. Each point represents the average of 5 measurements on the same hearts as those used in Fig. 1

groups of animals were treated with 0.05 mcg. per milliliter of ryanodine in Krebs solution for one hour after which the hearts were washed free of the drug and the interval-tension curves constructed.

Fig. 2 shows the interval-tension curves of the heart muscles after treatment with ryanodine. No tension was recorded over the Woodworth range but good contractility with undiminished tension was observed in the Bowditch range of the two control groups (*VIH* strain and *BIO 82.62*)

weight 135 ± 18 mg was later added to serve as appropriate age controls for the BIO 14 6 hamsters with severe congestive heart failure The weight of the ventricles given above does not include the weight of the triangular shaped muscle strip used for the measurement of tension Since the body and heart weights exhibited some variation among the different groups of animals and in order to obtain comparable values in the measurements of contractile tension strips of about the same size and shape were dissected from the right ventricular wall The average dimensions (width at the base × stretched length in millimeters) were as follows 5 6 × 11 7 for the NIH strain 6 5 × 11 8 for BIO 82 62* 5 4 × 15 1 for BIO 14 6 and 5 5 × 15 0 for the age control animals.

The animals were killed by exsanguination the chest was opened and a triangular shaped strip of muscle was excised from the free wall of the right ventricle beginning at the pulmonary artery The muscles were suspended in a lucite bath by attaching the pulmonary artery by means of a thin (26 gauge) stainless steel tubing to a Statham transducer (G7A-0 15-350) The narrow base of the muscles was tied to a lucite bar firmly attached through rack and pinions to the transducer One electrode was attached to the base of the muscle the other to the pulmonary artery Ringer Krebs solution[3] was used throughout the experiment vigorously gassed with a mixture of 95 per cent oxygen and 5 per cent carbon dioxide The temperature of the bath was kept between 21 and 22° C in order to avoid spontaneous rhythmicity which usually occurs above 23° C The transducer was coupled through a Brush Electronics (Model BL 520) amplifier to a Brush (B2902A) oscillograph A Grass (Model S4) stimulator was used with a SIU4 stimulus-isolation unit at intervals longer than 10 seconds the stimulator was controlled by an external time clock

Results

The over all state of contractility of the cardiac muscle is best studied by measuring isometric tension over the widest possible frequency range for the contribution of the two basic constituents of contractility (BP and WP) varies widely with the frequency of stimulation Fig 1 shows the tension at various frequencies (expressed as interval between stimuli) in three groups of hamsters Group 1 normal golden hamsters (NIH strain) Group 2 young hamsters with cardiomyopathy (BIO 82 62) prior to the development of cardiac failure and Group 3 hamsters with cardiomyopathy (BIO 14 6) in the final stages of congestive heart failure. The interval tension curves of Groups 1 and 2 are similar They show the characteristic curve of a species endowed with both the BP and WP demonstrated by the rising tension at both ends of the curve The wide separation of the two phenomena leaves the middle frequencies with scarcely any contractile tension This is in contrast to rat cardiac muscle in which the tension in the middle frequency range is only slightly depressed due to a considerable overlap of the two phenomena.[1] The interval tension curve of the diseased hamster heart (Fig 1 *BIO 14 6*) shows a parallel course with the curves obtained from the two control groups, but only over the range of the WP (2 to 60 second interval) During the stimulus interval when the BP begins to develop in the normal animals (2 seconds and less) the curve of the diseased animals continues to decline as though the BP were missing in these hearts The interval tension curve of those animals serving as age controls for the BIO 14 6 group (see methods) is parallel to that of Groups 1 and 2 with an average tension of 1 8 gram at 0 5 second and 0 4 gram at 2 second intervals demonstrating that the BP is present in the old healthy hamsters and that the absence of BP in the diseased animals is not due to their advanced age

In order to determine whether the BP is absent in the diseased hearts, all three groups of animal hearts were treated with ryanodine It has been shown that this drug irreversibly destroys the WP but leaves the contractility produced by the BP intact.[1] In essence contractility remaining after treatment with ryanodine can be regarded as the result of BP alone. All hearts of the three

*Animals of the BIO 82.62 strain were supplied by the Trenton Experimental Laboratory Animal Company Bar Harbor Maine 04609.

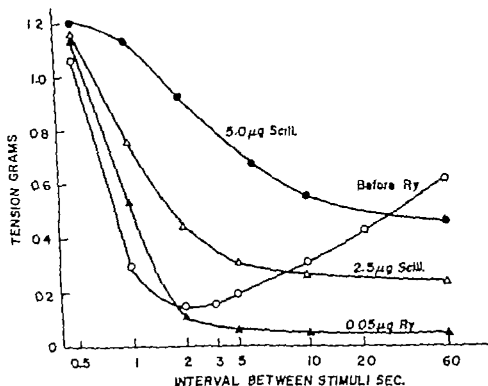


Fig. 4. Typical interval-tension relationship of the right ventricle of a normal hamster before treatment with ryanodine (*Before Ry*), after the addition of 0.05 mcg. per milliliter of ryanodine (*0.05 μg Ry*), same relationship upon addition of 2.5 mcg. per milliliter of scilliroside (*2.5 μg Scill.*) and after addition of 5.0 mcg. per milliliter of scilliroside (*5.0 μg Scill.*).

dine tension was the result of the WP only.

These experiments leave little doubt of the presence of a normal BP in the heart of young animals with cardiomyopathy which are still free of symptoms of cardiac incompetence, but they reveal its complete absence after the cardiac failure has reached its final stage.

Since the absence of BP in the heart of any species is without precedent, drugs known to influence the BI were tried first in order to gain some insight into the changes which led to the absence of this phenomenon. There is a long list of drugs and natural products known to do this,[6] but none is more potent than the cardiac glycosides. Scilliroside (Schering) was selected since it was found (unpublished observation) that this glycoside has a very powerful effect on rodent hearts which as is commonly known are rather insensitive to the preparations generally used. In order to avoid the complicating effect of the WP, the hearts were first treated with ryanodine. Fig. 4 shows an example of the interval tension relationships of a control animal (NIH strain) before and after treatment with ryanodine, and the effect of 2.5 and 5 mcg. per milliliter of scilliroside at steady state. As shown by the interval tension curves, the BI shifted toward the lower frequency range in a dose-dependent fashion as has already been demonstrated on frog hearts. Fig. 5 shows the results of similar experiments carried out on the hearts of the diseased animals. The interval tension curve before and after treatment with ryanodine shows the absence of BP (see Figs. 1 and 2). The addition of 2.5 mcg. per milliliter of scilliroside showed no measurable effect on the tension at any frequency. 5 mcg. per milliliter of scilliroside, although it increases the tension of the ryanodine treated muscle somewhat at every frequency, did not elevate the tension at the high frequencies, which would have indicated the return of the BI.

Potassium-free Krebs solution, which

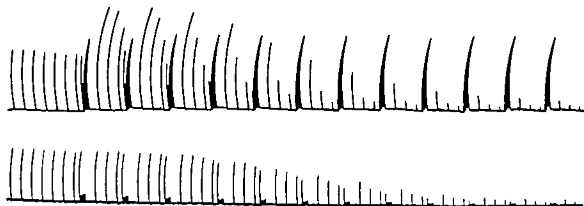


Fig. 3. Unretouched tracing of the isometric tension of the heart of the hamster with cardiomyopathy without cardiac failure (*BIO 8 62*) (upper tracing) and the hamster with cardiac failure (*BIO 14 6*) (lower tracing). At the beginning of the tracing 0.05 mcg. per milliliter of ryanodine was added to the bathing solution of both muscles. For a detailed description see text.

The hearts of the animals with congestive failure, on the other hand, developed no tension over the entire frequency range, showing that all tension exhibited by the hearts of these animals before ryanodine treatment was produced by the WP. The interval tension curve of the diseased animals (Fig. 1) is thus the first record of a pure WP undistorted by the presence of the BI, and its general course is in agreement with the one predicted.[1]

The difference in contractile activity of the hearts before and after the development of cardiac failure is shown in Fig. 3 by a pair of original tracings. Two extreme frequencies of stimulation were used alternately. A very low frequency (60 second interval) shows up on the tracings as individual contractions and represents contractility due to the WP. The high frequency stimulation (0.5 second interval) interposed alternately for 30 seconds shows up on a tracing as a solid column. The individual contractions cannot be seen very well due to the slow speed of the chart paper. This represents the contractility produced by the BI. Since 0.05 mcg. per milliliter of ryanodine was added to both muscles at the beginning of the tracing, the selective effect of the drug is shown as it slowly comes to completion (end of tracing).

The first seven contractions, paced at 60 second intervals, show that both muscles give comparable tensions in the Woodworth range. At exactly the middle of the eighth 60 second period, 60 fast beats were interposed by stimulating the muscle every 0.5 second. The first of the fast beats is still high, since it comes after a 30 second rest; the second is very small, being the first beat with a 0.5 second interval before it. From then on, while the still healthy animal increases its tension stepwise in the following 58 beats, the heart of the animal in failure shows no increase in contractility. This part of the tracings also clearly demonstrates that the development of the new steady state after a change of frequency occurs instantaneously in the case of the WI (lower tracing), but takes many contractions in the case of the BI, which still has not reached its maximum in 60 beats (upper tracing). The first beat with a 60 second interval immediately after the fast frequency stimulation is the strongest possible contraction,[4] or poststimulation potentiation seen only on the upper tracings. This is caused by the additive effect of the instantaneously reappearing WP and the slowly disappearing BI. On the lower tracings in the same position only a normal sized contraction is seen, corresponding to a 60 second interval (WP) without any sign of the slowly disappearing BP. If the tracing is followed from this point, the continuous disappearance of the WI due to the effect of ryanodine is obvious. Meanwhile the height of the tension produced by the intermittent high frequency stimulation attests to the presence of an undiminished BP in the healthy animals (upper tracing). The tension produced by the heart of animals with congestive failure is completely abolished at both frequencies during ryanodine treatment, showing that all preryano-

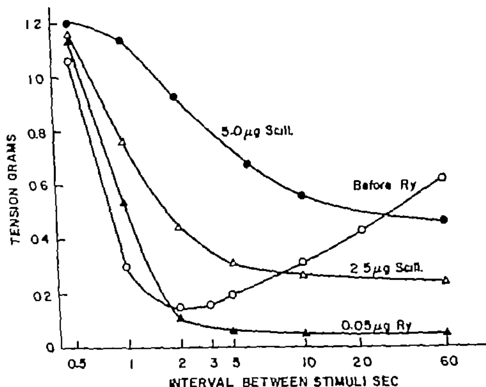


Fig. 4 Typical interval-tension relationship of the right ventricle of normal hamster before treatment with ryanodine (*Before Ry*) after the addition of 0.05 mcg per milliliter of ryanodine (*0.05 μg Ry*) same relationship upon addition of 2.5 mcg. per milliliter of scillirosside (*2.5 μg Scill.*) and after addition of 5.0 mcg. per milliliter of scillirosside (*5.0 μg Scill.*)

dine tension was the result of the WI only

These experiments leave little doubt of the presence of a normal BP in the heart of young animals with cardiomyopathy which are still free of symptoms of cardiac incompetence, but they reveal its complete absence after the cardiac failure has reached its final stage.

Since the absence of BP in the heart of any species is without precedent, drugs known to influence the BP were tried first in order to gain some insight into the changes which led to the absence of this phenomenon There is a long list of drugs and natural products known to do this, but none is more potent than the cardiac glycosides. Scilliroside (Schering) was selected, since it was found (unpublished observation) that this glycoside has a very powerful effect on rodent hearts, which as is commonly known are rather insensitive to the preparations generally used In order to avoid the complicating effect of the WP the hearts were first treated with ryanodine. Fig 4 shows an example of the interval-tension relationships of a control animal (NIH strain) before and after treatment with ryanodine, and the effect of 2.5 and 5 mcg per milliliter of scilliroside at steady state. As shown by the interval tension curves the BP shifted toward the lower frequency range in a dose-dependent fashion as has already been demonstrated on frog hearts. Fig 5 shows the results of similar experiments carried out on the hearts of the diseased animals. The interval tension curve before and after treatment with ryanodine shows the absence of BP (see Figs. 1 and 2) The addition of 2.5 mcg per milliliter of scilliroside showed no measurable effect on the tension at any frequency 5 mcg per milliliter of scilliroside although it increases the tension of the ryanodine treated muscle somewhat at every frequency did not elevate the tension at the high frequencies, which would have indicated the return of the BP

Potassium-free Krebs solution which

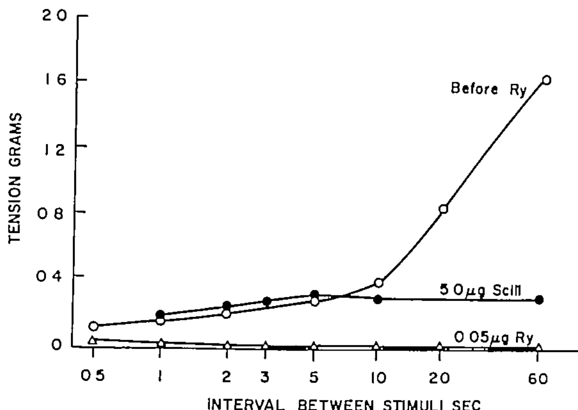


Fig 5 Typical interval-tension relationship of the right ventricle of a hamster with cardiomyopathy (*BIO 14 6*) with severe cardiac failure before treatment with ryanodine (*Before Ry*) after the addition of 0 05 mcg. per milliliter of ryanodine (*0.05 µg Ry*) and the same relationship after addition of 5 0 mcg per milliliter of scillirosıde (*5.0 µg Scill*) Since upon the administration of 2.5 mcg per milliliter of scillirosıde no measurable change occurred in the interval tension relationship observed after treatment with ryanodine (*0.05 µg Ry*) the same curve also describes the effect of 2.5 mcg per milliliter of scilliroside.

has an effect on the BP very similar to that of the glycosides [5] was also tried with identical results. Unimportant changes in contractility were observed across the whole frequency range even upon extreme potassium deprivation which finally produced contracture

Discussion

The following hypothesis was advanced for the explanation of the WP based on experiments made on isolated skeletal and heart muscles.[1] Muscle fibers contain a large supply of calcium that is restricted in its movement. A fraction of this calcium is altered during the rest interval so that it can enter and trigger the contractile proteins upon depolarization of the membrane The amount of calcium thus taking part in the electromechanical coupling is dependent on the duration of the rest interval and on the nature of the muscle The release of calcium yielding one full contraction requires a rest interval of about one second in the case of skeletal muscle, while the time required to accomplish the same is about one minute for the heart muscle [1] Due to the sluggish release of calcium in cardiac muscle the role of the WP is very limited in vivo because of the relatively short rest periods. This probably explains why animals without WP that either naturally do not have it or were deprived of it artificially by injection of ryanodine [1] can keep up a normal circulation The relative unimportance of the WP has also been demonstrated in the hamsters with cardiomyopathy which were in frank cardiac failure in spite of an undiminished WP Thus at a physiological heart rate the mechanism mainly responsible for producing the contraction is the BP This is why the hearts of all animals exhibit this phenomenon and when it is absent the heart can no longer support life as was observed in the case of the hamsters in the terminal stage of cardiac failure.

The underlying mechanism by which the BP regulates the contractility of the heart is not fully understood Some experimental

facts collected over the years, however have enabled us at least to formulate a theory giving a possible reason for the absence of BP in these hamsters. The most obvious quality of the heart of animals possessing only the BP is the dependence of contractility upon the concentration of the extracellular calcium to such a degree that a sudden change in its concentration during the course of a contraction influences the final outcome of the same beat.[4] This shows a direct involvement of the extracellular calcium in initiating the contraction in the Bowditch range. Another obvious quality of the heart in this range is that the contractile tension increases as the frequency increases, in other words, every frequency is characterized by a certain amount of tension (Fig 2) The development of this characteristic tension upon a change of frequency takes time. The greater the difference between the old and new frequency the longer it takes to reach a new steady state. When changing from 60 to 0.5 second intervals (Fig 3 upper tracing) the tension rises within 60 contractions from almost zero tension to a level which is still not that which would have been reached had more time been made available. During the development of the steady state of tension there is a parallel change in the intracellular potassium content of the muscle. The adjustment of the intracellular potassium is thought to take place in the following way.[10] During every contraction the muscle loses some potassium but regains the same amount by an active process from outside during the rest interval. Upon increase of frequency the loss of potassium occurs more often, and because of the shortened rest intervals the return transport of potassium also decreases, as a result there is a net loss of potassium The intracellular potassium decreases in the following beats, until finally the potassium influx becomes equal to the efflux, so that a new steady state of intracellular potassium content is achieved. Thus there is a characteristic level of intracellular potassium for every frequency of stimulation. The higher the rate of stimulation is, the lower the steady state of intracellular potassium. It is thus possible that the primary occurrence upon a change of frequency is a change in intracellular potassium and that the change in contractility is the consequence thereof This would seem to be probable, since it was found that a decrease in intracellular potassium without any change in frequency by reducing extracellular potassium or by the use of cardiac glycosides[1] (Fig 4) increased contractility and that a net uptake of potassium by the heart, again without any change of frequency decreased the tension. How a decrease in intracellular potassium can bring about an increased contraction upon depolarization raises further difficulties. It had been shown originally that as the tension increased upon increase of frequency the amount of calcium per beat entering the fiber also increased.[11] This would have furnished a simple explanation for the increased contractility However a more recent study[12] shows that there is no increase in calcium flux upon increased frequency If the latter is correct we must suppose that the decreased intracellular potassium itself renders the actomyosin more sensitive to the same amount of calcium. Whichever is the case the important point for the purpose of this discussion is that the increase of tension produced by increased frequency is the result of two consecutive steps, namely a decrease of intracellular potassium and the entry of calcium into the fiber Consequently the absence of the BP could be the result of a malfunction of either step Due to the restricted number of animals available in the terminal stage of cardiac failure we were able to test only the functional state of the potassium mechanism Lowering the intracellular potassium with cardiac glycosides (Fig 4) or decreasing the extracellular potassium which resulted in increased contractility in the control hearts at the same frequency did not bring back the missing BP in the failing heart, although this was not due to lack of response upon change of intracellular potassium brought about by these interventions. Their effectiveness was demonstrated by the slowing of relaxation and finally at the toxic stage by the appearance of contractures. But the decrease of intracellula potassium caused by these interventions did not give rise to increased contractility in the Bowditch range, probably because of failure in the

next step in these events namely lack of influx of extracellular calcium during depolarization

In support of this possibility it should be mentioned that these hearts are able to give full contractions at the very low frequencies at which all the calcium needed for the electromechanical coupling originates from bound sources (Fig 1) From whatever source it comes once sufficient calcium enters the fiber it contracts well which shows that all the following steps in the contraction cycle namely the shortening of the contractile protein energy transfer sequestration of calcium and the relaxation of actomyosin proceed normally Thus we see a heart with good contractile properties at low frequencies but without a BP in the physiological range A heart muscle with these characteristics cannot function adequately It cannot increase the cardiac output to an appreciable degree by increasing the heart rate because this leads to decreased contractility (Fig 1) On the other hand a slower heart rate which would increase contractility would diminish the output by decreasing the minute volume

The hypothesis that the cardiac glycosides exert their beneficial effect through a mechanism involved in BP[6,7] was further supported by the finding that the glycosides have no therapeutic effect in the absence of BI This means that at the terminal phase of cardiomyopathy during which the need for the action of glycosides would be the greatest their effectiveness seems to be lowest [14] The reason is that the glycosides working through the potassium mechanism obviously do not have an effect on the permeability of the membrane toward the influx of extracellular calcium which seems to be the primary cause of the cardiomyopathy in these animals

According to this hypothesis the change that takes place in these animals later in life leading to a fatal cardiac failure is a complete impermeability of the membrane to the entrance of free extracellular calcium during the depolarization of the membrane This is not without precedent among the contractile tissues. In fact, this is the way the skeletal muscle functions under physiological conditions since it does not use extracellular calcium for electromechanical coupling at all [1] The skeletal muscle functions very competently for hours in a calcium free medium for it has a very efficient WP which can supply enough calcium from bound sources at any frequency including tetanus In contrast to this as the membrane of the hamster with cardiomyopathy becomes impermeable to extracellular calcium the animal fails to compensate for this by increasing the efficiency of the release of calcium from bound sources as shown by the finding that even at the terminal stage of the disease the WP is not more efficient than that of the normal animal (Fig 1)

Summary

The interval tension relationship of right ventricular muscles of normal hamsters was compared to that of hamsters with hereditary cardiomyopathy with or without congestive heart failure. The contractility of the heart of animals with cardiomyopathy without circulatory insufficiency did not differ from that of the normal animals at any frequency The cardiac muscle of animals with severe congestive heart failure showed normal contractility at a low frequency of stimulation (range of the Woodworth phenomenon) but did not show the increased contractility upon high frequency stimulation (Bowditch phenomenon) seen in all other animals. Ryanodine which eliminates only the contractility caused by the Woodworth phenomenon abolished the contractility of the hearts of animals with congestive failure over the whole frequency range Cardiac glycosides which are known to potentiate the Bowditch phenomenon were ineffective on the cardiac muscle of animals without Bowditch phenomenon The probable cause of cardiac failure in hamsters with hereditary cardiomyopathy is discussed

The authors are greatly indebted to Dr Edna Bajusz of the Bio-Research Institute for his generous gift and careful selection of the hamsters with congestive heart failure (BIO 14 6)

REFERENCES

1 Hajdu, S.: Mechanism of the Woodworth staircase phenomenon I heart and skeletal muscle, Amer J Physiol 216:206, 1969
2. Bajusz, E.: Hereditary cardiomyopathy A new

disease model, Amer. Heart J 77:686, 1969
3. Krebs, H. A., and Henseleit, K.: Untersuchung ueber die Harnstoffbildung im Tierkoerper Hoppe Seyler Z. Physiol. Chem. 210:33, 1932.
4. Woodworth, R. S. Maximal contraction, staircase contraction, refractory period, and compensatory pause of the heart, Amer. J Physiol. 8:213 1902.
5. Hajdu, S. Bioassay for cardiac active principles based on the staircase phenomenon of the frog heart, J Pharmacol. Exp. Ther 120:90, 1956.
6. Weidmann, S. Effect of increasing the calcium concentration during single heart-beat, Experientia 15:128, 1959
7. Hajdu, S. Mechanism of staircase and contracture in ventricular muscle, Amer J Physiol. 174:371, 1953
8. Vick, R. L., and Kahn, J B., Jr. The effect of ouabain and veratridine on the potassium movement in the isolated guinea pig heart, J Pharmacol. Exp. Ther 121:389 1957
9. Sarnoff S. J Gilmore, J P McDonald R. H Jr and Mansfield, P B.: Relationship between myocardial K balance, O_2 consumption and contractility Amer J Physiol. 211:361 1966.
10. Leonard E., and Hajdu, S.: Action of electrolytes and drugs on the contractile mechanism of the cardiac muscle cell, Handbook of Physiology Section 2, Vol. 1 Baltimore, 1962 The Williams & Wilkins Company p. 174.
11. Niedergerke, R., and Harris, E. J: Accumulation of calcium (or strontium) under conditions of increasing contractility Nature (London) 179 1068, 1957
12. Winegard, S., and Shanes, A. M: Calcium flux and contractility in guinea pig atria, J Gen. Physiol. 45:371 1962.
13. Haacke, H., Luellmann, H., and van Zwieten, P A.: Calcium metabolism in atrial tissue during frequency potentiation and paired stimulation, Arch. Ges. Physiol. 311 113 19 0.
14. Burch, G. E., and DePasquale, N P: Heart muscle disease, Disease-a Month, Chicago, May 1968, Year Book Medical Publishers, Inc., p. 59.

Congestive heart failure following chronic tachycardia

Henry Neal Coleman III M.D
Roger R Taylor M D
Peter E. Pool M D
Gerald H Whipple M.D
James W Covell M D
John Ross Jr M D
Eugene Braunwald M D
Bethesda Md Boston Mass and San Diego Calif

The syndrome of chronic congestive heart failure has been associated with alterations in the function of a number of organ systems [1] the autonomic nervous system [2] and the peripheral circulation [3] However the limitations imposed by assessing cardiac function in the classical hemodynamic terms of pressure and flow have made it difficult to assess the contractile state of the myocardium and specifically to define the myocardial component of the congestive heart failure (CHF) syndrome However it has now been demonstrated both in studies of isolated heart muscle[4] and in the intact ventricle [5] that the contractile state of the heart can be characterized effectively in terms of myocardial force velocity relations. This approach has made it feasible to characterize myocardial function of the chronically failing heart in quantitative terms.

By characterizing force-velocity relationships of papillary muscles obtained from cats with pulmonary artery constriction and CHF Spann and co-workers[6] demonstrated depression of the myocardial contractile state In contrast, Taylor Covell and Ross [7] utilizing force-velocity relations derived from isovolumic left ventricular contractions demonstrated that the syndrome of CHF following the production of a large aortocaval fistula was associated with normal left ventricular contractility The object of the present investigation was to characterize the contractile state and energy stores of the heart in a form of CHF which was induced by chronic ventricular tachycardia.

Methods

Induction of CHF The details of the surgical procedure and the hemodynamic effects of chronic ventricular stimulation have been presented in preliminary form elsewhere.[8] In brief 18 mongrel dogs weighing from 13 to 24 kilograms had left

From the Cardiology Branch, National Heart Institute, National Institutes of Health, Bethesda, Md., and the Department of Medicine, Boston University School of Medicine, Boston, Mass.
Supported in part by Grant HE 12373 from the National Heart and Lung Institute.
Received for publication July 27 1970.
Reprint requests to Dr Eugene Braunwald, Professor and Chairman, Department of Medicine, University of California, San Diego, 225 West Dickinson St., San Diego, Calif 92103.

thoracotomy operations under pentobarbital anesthesia. Polyvinyl catheters filled with saline containing 18 mg. of heparin per liter were placed in the left atrium, right atrium, pulmonary artery, and descending thoracic aorta. Shielded stimulating electrodes were then sutured onto the left atrial appendage and the outflow tract of the right ventricle. The four catheters and four electrodes were exteriorized through individual dorsal intercostal percutaneous punctures. After wide incision of the pericardium around the body of the left ventricle, the thoracotomy was repaired.

Eight to ten days following the thoracotomy, stimulation of the heart via the ventricular electrodes was initiated in 10 animals at a frequency of 280 per minute with an external stimulator.* After 13 to 29 days of stimulation (average 19 days) six of the 10 dogs were judged to be in CHF on the basis of elevated left atrial pressures, a ventricular gallop sound, and/or evidence of fluid retention or recent gain in daily weight and they were studied. Studies were also carried out in the remaining four dogs without heart failure, as defined above, which had been stimulated for shorter periods of time (10 to 16 days). Eight dogs were not stimulated and served as sham-operated controls for determination of myocardial high energy phosphate stores.

Characterization of myocardial tension velocity relationships. The experimental procedure and the methods of calculation of the tension velocity relationships have been described previously in detail. Twenty-four hours following cessation of stimulator-induced ventricular tachycardia, animals were sedated with morphine sulfate (3 mg. per kilogram), promethazine (1.5 mg. per kilogram), and promazine (1.5 mg. per kilogram) by intramuscular injection and loosely restrained in the supine position. Aortic pressure was determined through the polyvinyl catheter in the thoracic aorta. Additional catheter insertions into the left ventricle and right intrapleural space were performed with the use of lidocaine local anesthesia. Left ventricular pressure was measured through a short PE 220 cannula attached directly to a pressure transducer.† This cannula was inserted into the left ventricle by direct percutaneous puncture with the use of a 19 gauge spinal needle as a trocar. Intraventricular pressure was referred to the level of the left ventricular cavity, as determined directly at the completion of each experiment. The first derivative of left ventricular pressure (dp/dt) was obtained with a differentiating circuit.

Intrapleural pressure was measured by inserting a Foley catheter through the right chest wall. Transmural left ventricular pressure obtained by subtracting the intrapleural pressure from the measured left ventricular pressure was used in calculating data from all isovolumic beats. All pressures were measured with Statham P23Db transducers and recorded on a multichannel oscillograph at a paper speed of 100 mm. per second. After recording basal pressures, cardiac output was measured by the indicator dilution method with the use of right atrial injection of indocyanine dye with aortic sampling through a cuvette densitometer.

Left atrial pacing was then instituted at a frequency of 150 per minute to match the rate of the previously studied normal dogs, and a rigid metal cannula with a rubber balloon mounted at its tip was passed through the left carotid artery and placed just above the aortic valve in the ascending aorta. Isovolumic contractions were then produced during expiration by rapid inflation of the balloon with 7 to 20 c.c. of saline delivered by a power injection synchronized by the electrocardiogram (ECG). Contractions were accepted for analysis if there was a smooth left ventricular pressure contour, an uninterrupted fall in left ventricular dp/dt following its peak, and a progressive decline in aortic pressure which indicated that left ventricular ejection had been completely prevented. A range of transmural end-diastolic pressures was obtained by rapid infusion of 50 ml. increments of previously exchanged blood.

Myocardial wall tension (T) was calculated from the formula

$$T = \frac{PR_i}{2h} \text{ Gm./cm.}^2$$

where P = transmural pressure in grams per square centimeter, R_i = internal radius

*Medtronic Model 5800, Medtronic, Minneapolis, Minn.

†Model 1602, Electronic Corp., Inc., Valley Stream, N. Y.

(centimeters) and h = wall thickness (centimeters) R was calculated with the assumption of a spherical model for the left ventricle The units of T grams per square centimeter are those of stress or force per unit area The terms tension and stress are used interchangeably Although the simplifying assumption of a spherical shape for the left ventricle ignores changes in shape which have been demonstrated to occur during isovolumic contraction the magnitude of the error involved is considered to be relatively minor [9,10] The left ventricular end-diastolic volume was derived from the transmural end-diastolic pressure and the pressure volume curve of the potassium chloride or anoxia arrested ventricle at the end of each experiment [5,7,11] The right ventricle was vented during this procedure and left ventricular volumes at any given left ventricular end-diastolic pressure were corrected for the influence of the distended right ventricle on the passive pressure-volume relationship of the left ventricle the method and errors involved have been described previously [10,11] The mass of the left ventricle was determined at the completion of each experiment and wall thickness was calculated assuming a symmetrical distribution around the left ventricular volume [5]

Contractile element velocity V_{CE} was calculated from isovolumic contractions with Hill's two-component model for muscle as described previously In these calculations the rate of elongation of the series elastic component (dl/dt) and V_{CE} were assumed to be equal in the isovolumic contraction V_{CE} was determined from the relationship

$$\frac{dp/dt}{K P} = dl/dt_{CE} = V_{CE}$$

in cm/cm/sec (circumferences per second) The value of 28 for K was used in all calculations in accord with values described in both dog ventricles and cat papillary muscle.[12,13] In each isovolumic beat wall tension and V_{CE} were calculated from measurements of dp/dt and transmural left ventricular pressure at 10 msec intervals until peak isovolumic pressure was reached

Biochemical characterization of heart failure Tissue samples for the determination of high-energy phosphate concentrations were obtained with the use of a drill biopsy technique which permitted freezing of tissue in liquid nitrogen-cooled isopentane within one second [14] Tissue samples were 2 mm in diameter and contained the entire thickness of the left ventricular wall Detailed descriptions of the methods used for the chemical determinations of total creatine creatine phosphate and adenosine triphosphate (ATP) have been published [15,16]

Results

Hemodynamic effects of chronic ventricular stimulation The hemodynamic status and physical findings in each of the six dogs with congestive heart failure are shown in Table I Average values for each variable are compared to values previously reported by our laboratory from a group of 15 normal animals studied with identical techniques.[5] Heart failure following chronic tachycardia was associated with a significant increase in left ventricular end-diastolic pressure (LVEDP) and end-diastolic volume (EDV) the occurrence of an abnormal ventricular gallop sound and accumulation of ascitic fluid in five of six animals. The average spontaneous heart rate aortic pressure and ratio of stroke volume (SV) to EDV were decreased while SV was maintained within normal limits These alterations were associated however with a significant increase in cardiac index Although left ventricular volume was increased there was no evidence of left ventricular hypertrophy when the ratio of left ventricular mass to body weight was examined This ratio refers to body weight at the time of study comparison of left ventricular weight to body weight prior to preparative surgery resulted in a small and not significant decrease in the ratio since body weight declined during the period of stimulation required to produce heart failure (average weight loss 1 4 kilograms)

Characterization of the mechanics of left ventricular contraction Following the measurement of hemodynamic variables, left atrial stimulation at a frequency of 150 per minute was begun and four to twelve isolated isovolumic contractions were produced in each dog Tension velocity

*Table I Congestive heart failure (CHF) following chronic tachycardia—hemodynamic observations**

Dog	Dog weight (Kg.)	LVEDP (mm. Hg)	LV EDV (ml.)	Heart rate (beats/min.)	Aortic pressure (mm. Hg)	Cardiac output (ml./Kg./min.)	SV (ml.)	SV/EDV	LV weight/body weight	Ventricular gallop sound	Ascites
1	16.0	24	50	93	118/92	193	44	0.55	4.67	Present	Present
2	17.2	23	47	135	105/84	165	26	0.44	4.71	Present	Present
3	15.0	22	56	111	115/74	71	10	0.18	5.82	Present	Present
4	18.7	31	47	123	132/90	119	15	0.32	4.95	Present	Absent
5	20.45	30	30	123	125/85	186	17	0.29	6.06	Present	Present
6	20.8	31	66	103	145/82	129	28	0.33	6.12	Present	Present
Mean CHF S.E.M.	18.3 ±0.5	28 ±3	53 ±7	114 ±4	122/79 ±6/6	160 ±21	23 ±5	0.35 ±0.06	5.27 ±0.40	Present in 6 of 6	Present in 5 of 6
Mean of 15 normal control animals S.E.M.	19.3 ±0.6	7 ±0.6	40 ±2	125 ±9	132/94 ±3/4	194 ±8	20 ±1	0.50 ±0.03	5.25 ±0.00	Present in 0 of 15	Present in 0 of 15
p		<0.01	<0.01	<0.04	<0.001/<0.001	<0.05	—†	<0.05	—†	<0.001	<0.001

*LVEDP Left ventricular end-diastolic pressure; SV stroke volume; EDV end-diastolic volume; LV left ventricular; S.E.M. standard error of the mean. Dog weight represents preterminal weight. Cardiac output is based on the weight at the time of the study.
†Not significant.

relations derived from isovolumic contractions at two left ventricular EDP's for a typical experiment are shown in Fig 1. This inverse relationship established some 30 to 40 msec. after the onset of contraction and lasting until 40 msec. before peak tension development, was qualitatively similar to that described in normal dogs. The extrapolation of the two curves to the intercept on the ordinate was used to estimate maximal intrinsic velocity of muscle contraction (V_{max}) which was not detectably altered by a change in left ventricular EDP in these experiments. Values for V_{max} in the six animals with heart failure ranged from 1.93 to 2.79 circumferences per second and averaged 2.37 ± 0.4 circumferences per second. This value was significantly depressed ($p < 0.001$) when compared to a V_{max} of 3.00 ± 0.03 (range 2.7 to 3.5) in 15 normal dogs studied in a similar manner. The time to peak pressure averaged 135 ± 3 msec. and was not significantly different from the normal value of 139 ± 3 msec.

The intercept of tension velocity curves on the abscissa defines peak isovolumic tension (P_o). In the typical experiment illustrated in Fig 1 increasing LVEDP from 7 to 22 mm Hg was associated with similar directional changes in P_o thus demonstrating the typical effects of the Frank-Starling mechanism. Comparisons of P_o from dogs with heart failure to that from normal control animals were made with observations grouped according to calculated end-diastolic tension (EDT) and LVEDP. Fig 2 demonstrates this relationship between P_o and EDT for the two groups. All individual points from which the mean value ±1 S.E.M. (open squares) was derived in the dogs with heart failure are shown. Every observation in five of the six dogs studied was depressed. In dog No. 6, however, the relationship between LVEDT and peak isovolumic tension was normal for four individual observations. This animal had had the longest period of stimulation (29 days) and it is of possible significance that the spontaneous arterial systolic pressure was substantially higher than that of the other five animals, and the left ventricular weight was the largest. The mean relationship between LVEDT and peak isovolumic tension appeared flattened and depressed relative to that of control

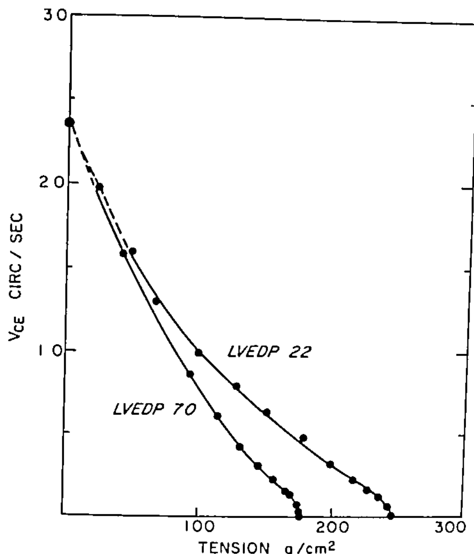


Fig 1 Tension-velocity relationships derived from isovolumic contraction of two left ventricular end-diastolic pressures (LVEDP) (Dog No 1)

animals (Fig 2) and the dogs with heart failure demonstrated a significant ($p < 0.001$) depression in the average level of peak isovolumic tension generated from a given LVEDT Similar results were obtained by relating Po to LVEDP

In the four dogs studied after 10 to 16 days of ventricular stimulation but prior to development of elevated LVEDP fluid retention or a protodiastolic gallop sound V_m was normal in two (3 35 and 4 34 circumferences per second) and diminished in two animals (2 65 and 2 56 circumferences per second) The relationship between LVEDT and peak isovolumic tension was within normal limits in one dog and depressed in the other three dogs. These findings indicate that dogs stimulated for insufficient time to produce heart failure also may have depression of contractility and probably represent transitional states in development of heart failure

Myocardial high-energy phosphate concentrations Following the characterization of the myocardial contractile state rapid transmural biopsy of the left ventricle was performed under hexobarbital anesthesia Myocardial high-energy phosphate and total creatine concentrations were assessed in the samples obtained from the six animals with congestive heart failure and these values were compared with those obtained from eight dogs in which operation with the placement of catheters and electrodes was performed These animals were not stimulated and thus formed a sham-operated group of controls (Table II) Myocardial total creatine concentrations were significantly decreased by an average of 34 per cent in dogs with heart failure

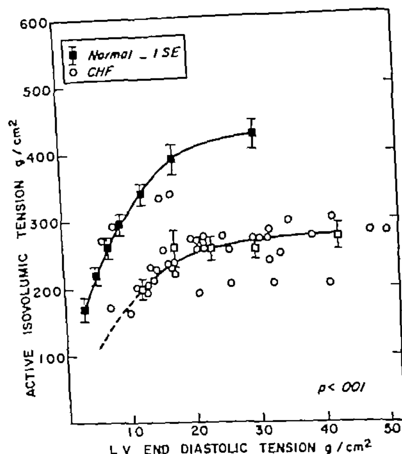


Fig. 2. Comparison of the left ventricular end-diastolic tension-active isovolumic tension relationships in dogs with congestive heart failure (open circles) and in normal control dogs (closed squares).

*Table II. Biochemical characterization of CHF induced by chronic tachycardia**

Preparation	*Total creatine (μM/Gm.)*	*Creatine phosphate (μM/Gm.)*	*ATP (μM/Gm.)*	*CP + ATP (μM/Gm.)*
Mean CHF (6 dogs) ± S.E.M.	13.8 ± 0.6	7.1 ± 0.6	5.43 ± 0.65	12.6 ± 1.3
Mean sham-operated (8 dogs) ± S.E.M.	21.3 ± 0.8	9.0 ± 0.6	6.44 ± 0.25	15.5 ± 0.8
Statistical significance:	$p < 0.005$	$p < 0.05$	$p < 0.10$	$p < 0.05$

*Abbreviations: CHF, congestive heart failure; ATP, adenosine triphosphate; CP, creatine phosphate; and S.E.M., standard error of the mean.

Total myocardial high-energy phosphate concentrations, i.e., the sum of creatine phosphate and ATP, also were significantly decreased by an average of 17 per cent.

Discussion

Following the induction of heart failure by chronic ventricular tachycardia, significant increases in average LVEDP and LVEDV occurred while aortic pressure, spontaneous heart rate, and the average ratio of stroke volume/EDV were all decreased. These alterations were accompanied by a small (but significant) increase in cardiac output. The latter finding is consistent with the hypothesis that the

tachycardia interfered with the hemodynamic function of the ventricles as a pump and that as a consequence the total blood volume became greatly augmented during the period of electrical stimulation Following discontinuation of stimulation it is presumed the augmented blood volume maintained the LVEDV at elevated levels and with a normal stroke volume raised the cardiac output to levels exceeding those existing during the period of stimulation

In contrast to the augmentation of cardiac output characterization of the mechanics of myocardial contraction demonstrated significant depression of left ventricular myocardial contractility This depression of contractility was characterized by a significant reduction in the estimated intrinsic velocity of contraction (V_m) a finding reported to be independent of load time and initial fiber length in isolated cardiac muscle[12] and in the intact heart [9] Thus this depression of contractile state was not influenced by the changes in fiber length and afterload observed in congestive heart failure Depression of myocardial contractility was further evidenced by a decrease in the level of active isovolumic tension development for any given end diastolic tension (Fig 2) Since both intrinsic velocity and active isovolumic tension development were found to be depressed the mean tension velocity relationship must also be depressed Thus the contractile state of the myocardium and the pumping action of the heart are not altered in a parallel direction in these animals with heart failure While cardiac index was sustained and even slightly elevated as a consequence of an elevation of LVEDV and the operation of the Frank Starling mechanism the contractile state of the myocardium was significantly depressed Additional evidence demonstrating that cardiac index and myocardial contractility are not always directly correlated is found in the recent work of Taylor Covell and Ross [7] who observed that the myocardial contractile state was normal in dogs with circulatory congestion myocardial hypertrophy and an elevated cardiac index following the creation of an aortocaval fistula. Conversely in experimentally produced myxedema, the myocardial contractile state was significantly depressed in the absence of signs of circulatory congestion.[1] Thus while congestive heart failure remains a useful term to describe a clinical syndrome the role of myocardial contractility in the production of this syndrome may vary

The finding of depressed contractility in these experiments is in accord with the results of Spann and associates[4] who reported a depression of force-velocity relationships of right ventricular papillary muscles obtained from cats with heart failure induced by pulmonary artery constriction Significant depression in contractility was also noted in muscle obtained from animals with cardiac hypertrophy produced by pulmonary artery constriction but without heart failure In the present experiments as well as in the studies on papillary muscles reported by Spann and associates [4] heart failure did not alter the time to peak tension This finding suggests that the duration of the active state is not changed while the depression in intrinsic velocity (V_m) reflects a reduction in the intensity of the active state Of note however is that heart failure produced by pulmonary outflow obstruction was associated with significant myocardial hypertrophy while the depression of the contractile state following chronic tachycardia occurred in the absence of detectable ventricular hypertrophy Thus while depression of contractility is present in both types of heart failure the absence of hypertrophy in heart failure following chronic tachycardia suggests that hypertrophy is not an essential feature in the etiology of the depressed contractile state. It is of interest that myocardial contractility was found to be depressed *after* the abnormal hemodynamic burden on the heart imposed by the tachycardia had been removed Thus the depression of myocardial function was not a transient phenomenon which ended with the termination of the period of ventricular tachycardia

Many investigations have been directed to an evaluation of myocardial energy stores in congestive failure These energy stores have been variably reported to be normal [17,18] slightly decreased [1] or moderately decreased [20] However the energy

stores which exist in the myocardium at any instant result from the relative balance between the processes of energy production and energy utilization. When an increased load is placed upon the heart, and myocardial hypertrophy has not occurred there exists an increased contractile effort per unit of myocardial mass and thus an increased demand for energy. Theoretically metabolic regulatory mechanisms will increase energy production to compensate for these changes, at least in part.

In the present investigation the ventricular tachycardia may be assumed to have greatly increased the energy demands per unit of myocardial mass and shifted the balance between energy supply and demand. This might explain the demonstration of small though significant, reduction in total myocardial high-energy phosphate concentrations. However it is interesting that these changes were found after discontinuation of the stimulation. Generally similar conclusions were reached in a recent study in which congestive heart failure was produced in cats by pulmonary artery constriction. Normal indices of energy production were found in mitochondria isolated from the right ventricles of these animals,[11] while total energy stores and myocardial contractility were depressed[4] in vivo. Energy stores of papillary muscles from the same hearts studied in vitro in which the workload was reduced were not significantly depressed. These differences were interpreted as an indication that an imbalance between energy production and utilization might account for the in vivo depression of myocardial energy stores.

The decreases in total myocardial creatine concentration which were observed are more difficult to explain. Creatine is synthesized primarily in the liver and subsequently transported to the heart where it must be taken up from the blood against a large concentration gradient by energy requiring processes. It is possible that increased energy requirements for contraction might deprive the concentrating mechanism of sufficient energy for its operation, or alternatively that hepatic synthesis of creatine may be depressed in congestive heart failure.

In summary in the heart failure state which persists following discontinuation of chronic ventricular tachycardia, left ventricular contractility was found to be depressed as characterized by reduction both in the intrinsic velocity of contraction and the active isovolumic tension development. This depression of the contractile state was accompanied by an elevated ventricular end-diastolic pressure and a reduction of the ratio of stroke volume to end-diastolic volume. These changes in the contractile state were associated with modest but significant depressions of myocardial total creatine and high energy phosphate concentrations.

These observations may be relevant to patients who experience ventricular tachycardia. While this arrhythmia rarely persists for periods as long as those employed in these experiments, ventricular tachycardia usually occurs in patients with impaired myocardial function and/or myocardial ischemia. Under these circumstances it is not unreasonable to suggest that the changes in myocardial mechanics and high energy phosphate stores observed herein may adversely affect cardiac function during and after the arrhythmia.

Summary

The mechanics of left ventricular contraction were analyzed in quantitative terms from isovolumic contractions in six dogs in which congestive heart failure developed following 13 to 29 days of chronic pacemaker-induced ventricular tachycardia. Twenty-four hours following cessation of stimulation heart failure was evidenced in the intact sedated dogs by elevated left ventricular end-diastolic pressures (average 28 mm Hg) ascites, and the presence of a protodiastolic gallop sound. Aortic pressure, heart rate and the ratio of stroke volume to end-diastolic volume were decreased while the ratio of left ventricular mass to body weight was unchanged and cardiac output was increased, presumably secondary to hypervolemia. Left ventricular function was substantially reduced, contractile element velocity tension relations were altered and V_{max} was significantly reduced (failure 2.37 ± 0.40 circumferences per second vs. control 3.0 ± 0.03). The maximum isovolumic tension development

for any given end-diastolic volume also was decreased in five of six animals. Left ventricular myocardial stores of creatine creatine phosphate, and adenosine triphosphate were significantly depressed These findings indicate that the syndrome of heart failure following chronic tachycardia characterized by elevated left ventricular end-diastolic pressure and ascites is associated with significant depression of the left ventricular contractile state and total energy stores.

REFERENCES

1. Friedberg C. K. Diseases of the heart Philadelphia 1966 W B Saunders Company
2. Chidsey C A Braunwald E. and Morrow A G Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure, Amer J Med 39:442 1966.
3. Zelis, R Mason D T and Braunwald E. A comparison of the effects of vasodilator stimuli on peripheral resistance vessel in normal subjects and in patients with congestive heart failure, J Clin. Invest 47:960 1968.
4. Sonnenblick E H Force-velocity relations in mammalian myocardium Amer J Physiol 202:931 1962.
5. Ross, J Jr Covell J W Sonnenblick, E. H and Braunwald E. Contractile state of the heart characterized by force-velocity relations in variably afterloaded and isovolumic beats, Circ. Res. 18 149 1966
6. Spann J F Jr Buccino R. A Sonnenblick E. H and Braunwald E Contractile state of cardiac muscle obtained from cats with experimentally produced ventricular hypertrophy and failure, Circ Res. 21:341 1967
7. Taylor R. R Covell J W and Ross, J Jr Left ventricular function in experimental aorto-caval fistula with circulatory congestion and fluid retention J Clin Invest 47:1333 1968.
8. Whipple, G. H Sheffield L T Woodman E G Theophilis, C and Friedman, S. Reversible congestive heart failure due to rapid stimulation of the normal heart Proc New Eng Cardiovasc. Soc. 20:39 1962
9. Taylor R. R. Ross, J Jr Covell J W and Sonnenblick E. H A quantitative analysis of left ventricular myocardial function in the intact sedated dog Circ. Res. 21:99 1967
10. Taylor R. R Covell J W Sonnenblick, E. H., and Ross, J Jr Dependence of ventricular distensibility on filling of the opposite ventricle Amer J Physiol 213:711 1967
11. Taylor R. R. Covell J W and Ross, J Jr Influence of the thyroid state on left ventricular tension velocity relations in the intact sedated dog J Clin. Invest. 48:775 1969
12. Forwand S. A. McIntyre, K. M Lipana, J G and Levine, H J Active stiffness of the intact canine left ventricle, Circ. Res. 19:970, 1966.
13. Sonnenblick E. H: The myocardial cell. Structure, function and modification by cardiac drugs, Philadelphia, 1966 University of Pennsylvania Press.
14. Pool P E. Norris, G F Lewis, R M and Covell J W A biopsy drill permitting rapid freezing J Appl. Physiol. 21:832 1968.
15. Pool P E. and Sonnenblick E. H The mechanochemistry of cardiac muscle. I The isometric contraction J Gen. Physiol 50:951 1967
16. Pool P E. Chandler B M Seagren, S. C. and Sonnenblick, E. H Mechanochemistry of cardiac muscle. II The isotonic contraction, Circ. Res. 22:465 1968.
17. Buckley N M and Tsuboi K. K. Cardiac nucleotides and derivatives in acute and chronic ventricular failure of the dog heart Circ. Res. 9:618, 1961
18. Olson, R. E Myocardial metabolism in congestive heart failure, J Chronic Dis. 9:442 1959
19. Pool P E. Spann J F Jr Buccino, R. A., Sonnenblick, E. H and Braunwald E. Myocardial high energy phosphate stores in cardiac hypertrophy and heart failure, Circ. Res. 21:365 1967
20. Fox, A. C. Wikler N S. and Reed, G E.: High energy phosphate compounds in the myocardium during experimental congestive heart failure. Purine and pyrimidine nucleotides, creatine, and creatine phosphate in normal and in failing hearts, J Clin. Invest. 44:202, 1965.
21. Sobel B E. Spann, J F Jr Pool P E., Sonnenblick E. H and Braunwald E. Normal oxidative phosphorylation in mitochondria from the failing heart, Circ. Res. 21:355 1967

Left ventricular power in man

Richard O. Russell, Jr., M.D.
C. McGavock Porter, M.D.
Morris Frimer, M.S.F.
Harold T. Dodge, M.D.
Birmingham, Ala.

Ventricular power is an expression of the rate at which the left ventricle does work. It is computed as a function of instantaneous pressure and velocity of ejection. Power is used to characterize the performance of other types of pumps, and peak power has been used to characterize the performance of motors and engines. Chapman, Baker, and Mitchell determined left ventricular power as a measure of left ventricular function in intact dogs with the use of ventricular volume data obtained by an angiocardiographic technique. Studies of left ventricular power in man have been reported by Bunnell, Grant, and Greene, who used ventricular volume data determined from biplane angiograms. Studies of left ventricular power in man have been performed by Hernandez, Greenfield, and McCall, by Greenfield and co-workers, and by Snell and Luchsinger[4] from measurements of aortic pressure and flow. These investigators computed blood flow from velocity, as measured by the aortic pressure gradient technique, and the aortic radius, as determined from angiograms. However, with these methods, it is not possible to determine ventricular power when mitral regurgitation or aortic stenosis is present. Furthermore, these methods do not allow one to relate ventricular power to chamber volume or chamber weight.

In the present studies, left ventricular power is computed as the product of left ventricular pressure and rate of change of left ventricular volume. Accordingly, it includes the parameters of pressure or resistance to ejection and rate of left ventricular ejection. Also, power as computed from left ventricular pressure and volume data in this study has made it possible to determine peak power values in patients with valvular heart disease including mitral insufficiency and aortic valve stenosis, and to relate these values to end-diastolic volumes and mass. Others have shown that the myocardial contractile state can be characterized in terms of rate of contraction and resistance to ejection.[5-8] Accordingly, ventricular power may be a more sensitive measure of myocardial performance than stroke volume or stroke work or the relationship of these parameters to end-diastolic volume (EDV). To our knowledge, this is the first time left ventricular power has been measured directly in patients with

From the Division of Cardiology of the Department of Medicine, University of Alabama, Birmingham, Ala.
Supported by United States Public Health Service Grant HE 1310 from the Department of Health, Education and Welfare and by Vocational Rehabilitation Grant RD-2219-M.
Received for publication Aug. 17, 1970.
Reprint requests to: Dr. Richard O. Russell, Jr., 1 1 7th Ave. South, Birmingham, Ala. 35233.

heart disease and the present study is an attempt to evaluate the significance of this parameter

Methods

Data from 39 patients who underwent right and left heart catheterization for evaluation of cardiovascular disease in the laboratories of the University Hospital or the Birmingham Veteran s Administration Hospital were analyzed for this study The procedure was explained to each patient prior to catheterization and informed con sent was obtained Ages of the patients ranged from 16 to 72 years There were 22 men and 17 women Patients were studied in supine position in the postprandial state. Studies were usually performed without sedation with the use of local anesthesia Biplane angiocardiograms were performed at the rate of 12 per second in 34 patients and 6 per second in 5 with a roll film changer* at 1 200 ma. 80 to 100 kv with exposure times of 18 to 30 msec. with triphasic x ray generators. In 24 pa tients pressure injection of roentgeno-graphic contrast medium (1 0 to 1 5 ml of 75 per cent sodium and meglumine diatri zoates per kilogram of body weight) was made into the left atrium via a transseptal catheter In these patients left ventricular pressure was recorded during filming by a separate catheter placed retrograde in the left ventricle In 14 patients, injection of contrast medium was into the left ventricle through a retrograde catheter pressure was recorded through the same catheter im mediately after injection and during film ing One patient with severe aortic insuf ficiency had injection of contrast medium into the ascending aorta with simultaneous measurement of left ventricular pressure through a separate catheter Cardiac rhythm during filming was normal sinus or atrial fibrillation with a relatively regular ventricular response. Films during a pre-mature ventricular contraction and the beat following were excluded from analysis, al though this exclusion does not assure com plete absence of postextrasystolic potentia tion of contractility in the subsequent beat

Left ventricular pressures were recorded through the above catheters with P23D or P23G strain gauges on a multichannel re corder and on magnetic tape together with an electrocardiographic monitoring lead and time of film exposure. The zero for pressure reference was taken as 10 cm. above the table top in all patients. In one patient left ventricular pressure was re corded with a catheter tip transducer (Statham SF 1) In this patient and five other patients not included in this study a comparison of left ventricular pressures recorded simultaneously through carefully flushed fluid filled catheters and catheter tip manometers demonstrated an average time lag of 0 03 second for the fluid-filled system On this basis, the left ventricular pressure curve recorded with the fluid filled system was advanced 0 03 second for com parison with volume curves, although small variations may occur from this presumed constant time lag

Left ventricular volumes were calculated from the area and length of the left ven tricle on the films by methods which have been previously described [11,12] The experi mentally determined ventricular volumes were plotted with respect to time in the cardiac cycle (Fig 1) A curve was gener ated by straight line fittings between data points by use of a digital computer This curve was smoothed with the use of a low pass filter with a cut-off frequency of 3 c p s. In this manner data were generated every 0 01 second The composite ventricu lar volume curve was related to the ven tricular pressure which was recorded during the angiocardiography with digitized values at every 0 01 second From these volumes and pressure curves, left ventricular power was calculated for each 0 01 second as the product of instantaneous pressure and rate of ejection as follows

$$\text{Power} = P \times dv/dt \times 0\,0136$$

where P = instantaneous pressure in milli meters of mercury dv = change in volume in milliliters each 0 01 second interval and 0 0136 is the constant to express the re-sults in gram meters per second The power values were plotted with respect to time within the heart cycle to construct power curves (Fig 1) A computer program is utilized for calculating power from the

*Elema-Schönander Stockholm, Sweden.

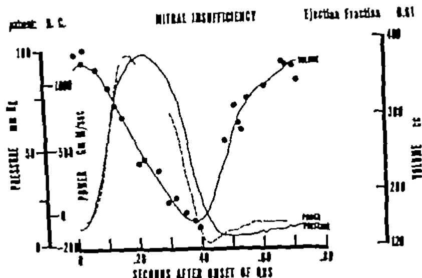


Fig. 1 Left ventricular pressure and volume data and power curve from a patient with mitral insufficiency. One solid line represents the left ventricular pressure (catheter tip manometer). The other solid line is the left ventricular volume curve which has been generated from the volume data points. The calculated left ventricular power curve is shown by dashed line.

digitized pressure-volume data. The peak power values are given in Table I.

Each patient's diagnosis is based upon both clinical and laboratory criteria. With the use of the left ventricular systolic ejection fraction (ratio stroke volume/EDV) patients were separated arbitrarily into two main groups. The first group of 24 patients had ejection fractions of 0.45 or greater. Twenty-two patients in this first group had mitral or aortic valve disease singly or in combination with varying degrees of severity and 2 had hemodynamically insignificant heart disease. The second group consisting of 15 patients, had left ventricular systolic ejection fractions of less than 0.45 and clinical diagnoses as listed in Table I. Patients in this group were considered to have impaired myocardial function although the majority also had concomitant valvular defects of varying severity. Three of the 15 patients had coronary artery disease demonstrated by coronary cineangiograms.

Results

Fig. 1 shows a left ventricular pressure curve, a volume curve, and a calculated power curve from a patient with severe mitral regurgitation.

Table I lists the patients with their diagnoses and pertinent hemodynamic data. One patient with insignificant mitral valve disease and one patient with a small ventricular septal defect had left ventricular peak power values of 434 and 540 Gm.M per second, respectively. These values in patients without significant heart disease are taken to represent "normal" values for left ventricular peak power.

Left ventricular peak power values ranged from 361 to 2,234 Gm.M. per second (mean 879 ± 403) in patients with valvular disease and normal ejection fractions and from 222 to 2,126 Gm.M per second (mean 621 ± 494) in patients with reduced ejection fractions, many of whom also had valvular heart disease. In Fig. 2 it is evident that in patients with mixed valve lesions, peak power values are similar in the subjects with depressed ejection fractions and in those with normal ejection fractions. These data show that resting subjects with chronic heart disease and mechanical overloads may have peak power values as much as 4 to 5 times normal.

Fig. 3 shows peak power plotted with respect to EDV. There is a wide scatter of all power values relative to EDV with a correlation coefficient of only 0.42 ($p < 0.01$). Similarly, there is a wide scatter of peak power values relative to left ventricular mass with only a slightly higher correlation coefficient with $r = 0.56$

heart disease and the present study is an attempt to evaluate the significance of this parameter

Methods

Data from 39 patients who underwent right and left heart catheterization for evaluation of cardiovascular disease in the laboratories of the University Hospital or the Birmingham Veteran's Administration Hospital were analyzed for this study The procedure was explained to each patient prior to catheterization and informed consent was obtained Ages of the patients ranged from 16 to 72 years There were 22 men and 17 women Patients were studied in supine position in the postprandial state Studies were usually performed without sedation with the use of local anesthesia Biplane angiocardiograms were performed at the rate of 12 per second in 34 patients and 6 per second in 5 with a roll film changer* at 1 200 ma 80 to 100 kv with exposure times of 18 to 30 msec with triphasic x ray generators. In 24 patients, pressure injection of roentgenographic contrast medium (1 0 to 1 5 ml of 75 per cent sodium and meglumine diatrizoates per kilogram of body weight) was made into the left atrium via a transseptal catheter In these patients left ventricular pressure was recorded during filming by a separate catheter placed retrograde in the left ventricle In 14 patients injection of contrast medium was into the left ventricle through a retrograde catheter pressure was recorded through the same catheter immediately after injection and during filming One patient with severe aortic insufficiency had injection of contrast medium into the ascending aorta with simultaneous measurement of left ventricular pressure through a separate catheter Cardiac rhythm during filming was normal sinus or atrial fibrillation with a relatively regular ventricular response. Films during a premature ventricular contraction and the beat following were excluded from analysis although this exclusion does not assure complete absence of postextrasystolic potentiation of contractility in the subsequent beat

Left ventricular pressures were recorded through the above catheters with P23D or P23G strain gauges on a multichannel recorder and on magnetic tape together with an electrocardiographic monitoring lead and time of film exposure The zero for pressure reference was taken as 10 cm. above the table top in all patients. In one patient left ventricular pressure was recorded with a catheter tip transducer (Statham SF 1) In this patient and five other patients not included in this study a comparison of left ventricular pressures recorded simultaneously through carefully flushed fluid filled catheters and catheter tip manometers demonstrated an average time lag of 0 03 second for the fluid filled system On this basis, the left ventricular pressure curve recorded with the fluid filled system was advanced 0 03 second for comparison with volume curves, although small variations may occur from this presumed constant time lag

Left ventricular volumes were calculated from the area and length of the left ventricle on the films by methods which have been previously described[11,12] The experimentally determined ventricular volumes were plotted with respect to time in the cardiac cycle (Fig 1) A curve was generated by straight line fittings between data points by use of a digital computer This curve was smoothed with the use of a low pass filter with a cut-off frequency of 3 c p s In this manner data were generated every 0 01 second The composite ventricular volume curve was related to the ventricular pressure which was recorded during the angiocardiography with digitized values at every 0 01 second From these volumes and pressure curves, left ventricular power was calculated for each 0 01 second as the product of instantaneous pressure and rate of ejection as follows

$$\text{Power} = P \times dv/dt \times 0\ 0136$$

where P = instantaneous pressure in millimeters of mercury dv = change in volume in milliliters each 0 01 second interval and 0 0136 is the constant to express the results in gram meters per second The power values were plotted with respect to time within the heart cycle to construct power curves (Fig 1) A computer program is utilized for calculating power from the

*Elema-Schönander Stockholm, Sweden.

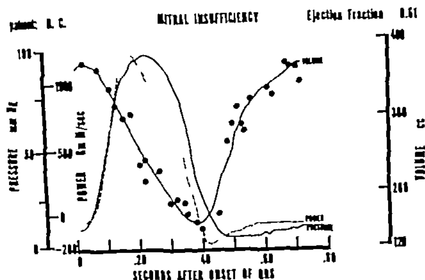


Fig. 1 Left ventricular pressure and volume data and power curve from a patient with mitral insufficiency One solid line represents the left ventricular pressure (catheter-tip manometer) The other solid line is the left ventricular volume curve which has been generated from the volume data points. The calculated left ventricular power curve is shown by dashed line.

digitized pressure-volume data. The peak power values are given in Table I

Each patient's diagnosis is based upon both clinical and laboratory criteria. With the use of the left ventricular systolic ejection fraction (ratio stroke volume/EDV) patients were separated arbitrarily into two main groups. The first group of 24 patients had ejection fractions of 0.45 or greater Twenty-two patients in this first group had mitral or aortic valve disease singly or in combination with varying degrees of severity and 2 had hemodynamically insignificant heart disease. The second group, consisting of 15 patients, had left ventricular systolic ejection fractions of less than 0.45 and clinical diagnoses as listed in Table I Patients in this group were considered to have impaired myocardial function although the majority also had concomitant valvular defects of varying severity Three of the 15 patients had coronary artery disease demonstrated by coronary cineangiograms.

Results

Fig 1 shows a left ventricular pressure curve, a volume curve and a calculated power curve from a patient with severe mitral regurgitation

Table I lists the patients with their diagnoses and pertinent hemodynamic data. One patient with insignificant mitral valve disease and one patient with a small ventricular septal defect had left ventricular peak power values of 434 and 540 Gm.M per second respectively These values in patients without significant heart disease are taken to represent "normal" values for left ventricular peak power

Left ventricular peak power values ranged from 361 to 2,234 Gm.M per second (mean 879 ± 403) in patients with valvular disease and normal ejection fractions and from 222 to 2 126 Gm.M per second (mean 621 ± 494) in patients with reduced ejection fractions, many of whom also had valvular heart disease. In Fig 2 it is evident that in patients with mixed valve lesions, peak power values are similar in the subjects with depressed ejection fractions and in those with normal ejection fractions. These data show that resting subjects with chronic heart disease and mechanical overloads may have peak power values as much as 4 to 5 times normal

Fig 3 shows peak power plotted with respect to EDV There is a wide scatter of all power values relative to EDV with a correlation coefficient of only 0.42 ($p < 0.01$) Similarly there is a wide scatter of peak power values relative to left ventricular mass with only a slightly higher correlation coefficient with $r = 0.56$

heart disease and the present study is an attempt to evaluate the significance of this parameter

Methods

Data from 39 patients who underwent right and left heart catheterization for evaluation of cardiovascular disease in the laboratories of the University Hospital or the Birmingham Veteran s Administration Hospital were analyzed for this study The procedure was explained to each patient prior to catheterization and informed con sent was obtained Ages of the patients ranged from 16 to 72 years. There were 22 men and 17 women Patients were studied in supine position in the postprandial state Studies were usually performed without sedation with the use of local anesthesia. Biplane angiocardiograms were performed at the rate of 12 per second in 34 patients and 6 per second in 5 with a roll film changer* at 1 200 ma 80 to 100 kv with exposure times of 18 to 30 msec. with triphasic x ray generators. In 24 pa tients pressure injection of roentgeno-graphic contrast medium (1 0 to 1 5 ml of 75 per cent sodium and meglumine diatri zoates per kilogram of body weight) was made into the left atrium via a transseptal catheter In these patients left ventricular pressure was recorded during filming by a separate catheter placed retrograde in the left ventricle In 14 patients injection of contrast medium was into the left ventricle through a retrograde catheter pressure was recorded through the same catheter im mediately after injection and during film ing One patient with severe aortic insuf ficiency had injection of contrast medium into the ascending aorta with simultaneous measurement of left ventricular pressure through a separate catheter Cardiac rhythm during filming was normal sinus or atrial fibrillation with a relatively regular ventricular response Films during a pre mature ventricular contraction and the beat following were excluded from analysis, al though this exclusion does not assure com plete absence of postextrasystolic potentia tion of contractility in the subsequent beat.

Left ventricular pressures were recorded through the above catheters with P23D or P23G strain gauges on a multichannel re-corder and on magnetic tape, together with an electrocardiographic monitoring lead and time of film exposure The zero for pressure reference was taken as 10 cm. above the table top in all patients. In one patient left ventricular pressure was re-corded with a catheter tip transducer (Statham SF 1) In this patient and five other patients not included in this study a comparison of left ventricular pressures recorded simultaneously through carefully flushed fluid filled catheters and catheter tip manometers demonstrated an average time lag of 0 03 second for the fluid filled system On this basis the left ventricular pressure curve recorded with the fluid-filled system was advanced 0 03 second for com parison with volume curves, although small variations may occur from this presumed constant time lag

Left ventricular volumes were calculated from the area and length of the left ven tricle on the films by methods which have been previously described[11,12] The experi mentally determined ventricular volumes were plotted with respect to time in the cardiac cycle (Fig 1) A curve was gener ated by straight line fittings between data points by use of a digital computer This curve was smoothed with the use of a low pass filter with a cut-off frequency of 3 c p s In this manner data were generated every 0 01 second The composite ventricu lar volume curve was related to the ven tricular pressure which was recorded during the angiocardiography with digitized values at every 0 01 second From these volumes and pressure curves left ventricular power was calculated for each 0 01 second as the product of instantaneous pressure and rate of ejection as follows

$$\text{Power} = P \times dv/dt \times 0\ 0136$$

where P = instantaneous pressure in milli meters of mercury dv = change in volume in milliliters each 0 01 second interval and 0 0136 is the constant to express the re-sults in gram meters per second The power values were plotted with respect to time within the heart cycle to construct power curves (Fig 1) A computer program is utilized for calculating power from the

*Elema-Schönander Stockholm, Sweden.

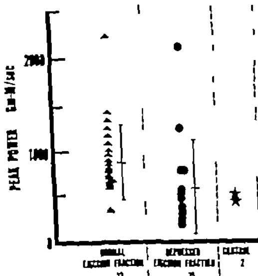


Fig. 2. Bar graph of the range of peak power values for patients with valvular disease having normal ejection fractions, for patients with depressed ejection fractions, and for the two control patients. Note the overlap of values in patients with normal and depressed ejection fractions.

($p < 0.01$) (Fig. 4). In Fig. 3 it is apparent that the patients with depressed ejection fractions have lower power values with respect to EDV. Higher peak power values were observed in subjects with normal ejection fractions at any particular EDV. The regression line in Fig. 3 relates peak power and EDV only in subjects with a normal ejection fraction. Patients with depressed ejection fractions and large EDV's relative to peak power values fall to the right of the regression line. Thus, the patients with low stroke volumes relative to EDV also have low peak power values relative to EDV.

As described in previous publications[14,15] and as discussed later, the systolic ejection fraction can be used as an index of myocardial performance. Accordingly, peak power values were related to systolic ejection fraction to determine to what extent peak power per se could be used to evaluate myocardial performance (Fig. 5). Peak power per se correlates poorly with the systolic ejection fraction ($r = 0.38$, $p < 0.01$) and does not provide a useful index to myocardial performance.

However, when peak power is normalized for the EDV in each patient, the correlation coefficient with systolic ejection fraction is 0.73 ($p < 0.01$). Thus, normalized peak power value tends to separate the patients with normal ejection fractions from those with depressed ejection fractions (Fig. 6). Similarly, when peak power is normalized for left ventricular mass, a relationship similar to that of peak power/EDV and ejection fraction exists (Fig. 7).

Fig. 8 further delineates the separation between patients with normal ejection fraction and those with depressed ejection fraction. Peak power/EDV in patients with normal ejection fraction was 4.53 ± 1.23 Gm M per second per cubic centimeter, whereas in those with depressed ejection fraction this ratio was 2.03 ± 1.18. Peak power normalized for left ventricular mass gave values of 3.67 ± 1.16 Gm.M per second per gram in patients with a normal ejection fraction and 1.98 ± 0.86 Gm M per second per gram in those with a depressed ejection fraction.

Discussion

More conventional methods for evaluating left ventricular performance such as relating stroke volume or stroke work to EDV do not take into account the rate at which the volume is moved or at which the work is performed. Other studies concerned with evaluating ventricular performance or the contractile state of the myocardium by such measurements as the maximal rate of pressure rise or velocity of the contractile element have demonstrated the importance of time function in assessing myocardial performance.[4-6] The expression of power incorporates the element of time as it is the rate of performing work and accordingly is a function of instantaneous pressure and rate of ejection. The latter is, at least in part, a function of the velocity of contraction.[1]

The values taken to represent "normal" left ventricular peak power in this study (434 and 540 Gm M per second) are derived from patients with insignificant mechanical defects. These values for peak power in normal individuals agree with those determined by previous investigators using the pressure-gradient technique of measuring aortic blood velocity.[4-6] In the estimation of "normal" left ventricular peak power patients with significant mitral

*Table I. Hemodynamic data**

Patient and diagnosis	Heart rhythm†	Ejection fraction	EDV (c.c.)	MASS (Gm.)	Peak power (Gm. M./sec.)	Ratio PK P / EDV	PK P / MASS
Ejection fraction 0.45 or greater							
Control							
1 Small VSD	NSR	0 57	143	156	540	3 78	3 46
2 Insignificant MS and MR	NSR	0 67	98	108	434	4 43	4 05
Mitral stenosis							
3 Recurrent MS mod	AF	0 53	117	158	385	3 29	2 44
4 Mod MS, mild AI	NSR	0 62	120	208	361	3 01	1 74
5 Mod MS mild AI	AF	0 18	129	194	675	5 23	3 48
6 Sev MS mild MR	AF	0 57	1	244	655	3 70	2 68
7 Sev MS mild AI and MR	NSR	0 47	205	181	721	3 52	3 98
Volume overload							
8 Mod. MR and AI	NSR	0 48	195	326	716	3 67	2 20
9 Sev MR	NSR	0 57	294	364	1321	6 81	3 63
10 Mod AI mild MS	NSR	0 66	200	216	814	4 07	3 77
11 Mod. MR mild MS	NSR	0 53	192	192	646	3 37	3 36
12 Mod AI IHD hypertension	NSR	0 63	171	275	798	4 67	2 90
13 Mod MR	NSR	0 55	192	215	698	3 64	3 25
14 Mod. MR mild MS	NSR	0 70	191	214	1417	7 42	6 62
15 Sev MR	NSR	0 61	360	213	1243	3 45	5 84
16 Sev MR acute ruptured chorda tendinea	NSR	0 63	263	206	1078	4 10	5 23
17 S.E. Mitr mod MR and MS mod AI ASD	NSR	0 67	226	373	1028	4 55	2 76
18 Sev AI mod MR	NSR	0 56	425	426	2234	5 26	5 24
Aortic stenosis							
19 Mod. AS	NSR	0 51	174	291	878	5 05	3 02
20. Mod AS	NSR	0 46	125	261	910	7 28	3 49
21 Sev AS mod. AI	NSR	0 45	187	312	954	5 10	3 06
Mixed valvular disease							
22 Mod MS and AI	NSR	0 56	181	191	634	3 50	3 32
23 Mod. MS and AI mild AS	NSR	0 57	310	312	1162	3 75	3 72
24 Mod MS AS, and AI	AF	0 53	127	164	783	6 17	4 77
Ejection fraction less than 0.45							
Myocardial disease							
25 MYD mod. MS mild MR	NSR	0 18	389	335	382	0 98	1 14
26 MYD mild MR	NSR	0 41	293	286	795	2 71	2 78
27 MYD mild MR	NSR	0 36	149	216	280	1 92	1 30
28 MYD mod MR, IHD diffuse cor artscl	NSR	0 25	328	311	498	1 5	1 60
29 MYD mild MR	NSR	0 28	214	184	533	2 49	2 90
30 MYD sev MR, cor artscl. old MI	NSR	0 18	570	546	573	1 00	1 05
31 MYD mild MR	NSR	0 25	242	254	401	1 66	1 58
32 MYD mod. MR	NSR	0 19	460	265	548	1 19	2 07
33 MYD IHD cor artscl diabetes	NSR	0 17	220	191	340	1 55	1 78
34 MYD mod MR	NSR	0 21	61	208	222	0 85	1 07
35 MYD mod. MS	AF	0 43	87	114	231	2 66	2 03
36 MYD mild AS mod AR	NSR	0 27	438	443	1243	2 84	2 81
37 MYD mod. MR	NSR	0 12	530	405	357	0 67	0 88
38 MYD acute hypertension	NSR	0 38	154	228	787	5 11	3 45
39 MYD sev AI	NSR	0 42	646	650	21 6	3 29	3 27

*Abbreviations: AF, atrial fibrillation; AI, aortic insufficiency; AS, aortic stenosis; ASD, atrial septal defect; Cor Artscl, coronary arteriosclerosis based on coronary cineangiographic findings; EDV, end-diastolic volume; IHD, ischemic heart disease based on clinical and electrocardiographic findings; MASS, left ventricular mass; MI, myocardial infarction; Mod, moderate; MR, mitral regurgitation; MS, mitral stenosis; MYD, myocardial disease; NSR, normal sinus rhythm; PK P, peak power; S.E. Mitr, Starr-Edwards mitral valve; Sev, severe; SV, stroke volume; and VSD, ventricular septal defect.

†Heart rhythm at the time of angiocardiographic studies.

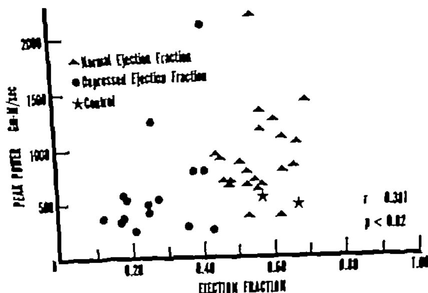


Fig. 5 Relation of peak power to ejection fraction in chronic heart disease. This illustrates the failure of peak power alone to separate patients with depressed ejection fraction from those with normal ejection fraction.

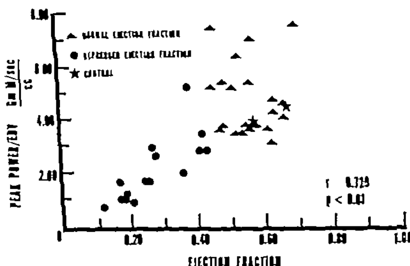


Fig. 6 Separation of patients by the ratio peak power/EDV as related to ejection fraction. The ratio peak power/EDV provides reasonably good separation of patients with normal ejection fraction and those with depressed ejection fraction. The linear correlation of this ratio with ejection fraction is = 0.73 ($p < 0.01$).

As shown in this study peak left ventricular power by itself also fails to adequately describe ventricular performance in chronic heart disease. The range of peak power in patients with a normal ejection fraction overlaps that of patients with a depressed ejection fraction

In this study the left ventricular systolic ejection fraction is used as an index of ventricular performance. In previous studies in man, the ejection fraction has been of demonstrable value in evaluating myocardial performance in patients with chronic heart disease.[illegible] Patients with myocardial disease have a low stroke volume relative to EDV i.e. a low ejection fraction.[14,17,23] Accordingly the left ventricle of patients with myocardial disease has a reduced stroke volume per unit EDV In earlier studies by Miller Kirklin and

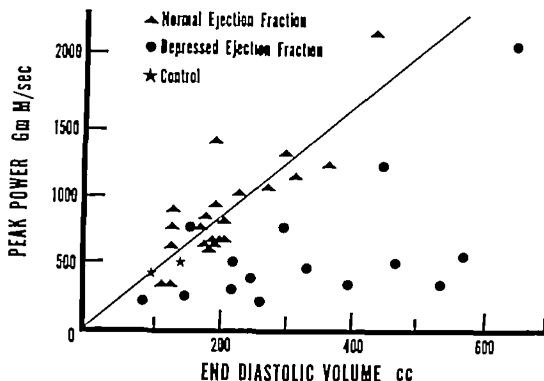


Fig 3 Peak power as a function of end-diastolic volume (EDV) There is a wide scatter of all power values related to EDV with a relatively poor correlation of 0.42 ($p < 0.01$) The patients in the lower right area of the graph have low peak power relative to left ventricular volume The line indicating the regression equation, $y = 31 + 4.24x$, where y is peak power and x is EDV relates only to patients with a normal ejection fraction. The power values from patients with depressed ejection fractions are below this regression line.

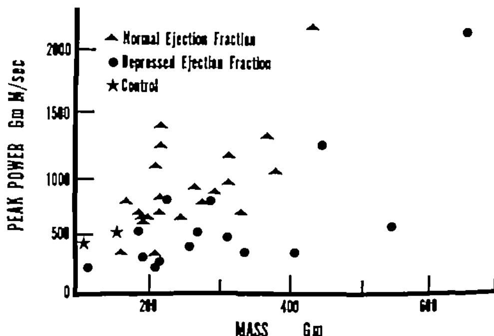


Fig 4 Relationship of peak power to left ventricular mass. As with EDV there is a wide scatter of peak power values relative to left ventricular mass values with a correlation coefficient of 0.56 ($p < 0.01$)

stenosis were omitted as left ventricular performance in such patients may be impaired [16,17] Left ventricular power has not been adequately studied in the normal left ventricle for obvious reasons.

Cardiac output or stroke volume, per se in subjects in a resting recumbent position is of limited value in defining myocardial performance in patients with a normal or a failing myocardium [18] Nor is systolic work alone useful in characterizing the functional state of the left ventricular myocardium [11,19]

cribed myocardial function in terms of milies of curves.[11] Depressed myocardial ction was characterized by low stroke rk relative to end-diastolic pressure and cordingly volume. Earlier Patterson per and Starling[18] had demonstrated low oke volumes relative to EDV with myo-rdial depression in acute studies. This is alogous to the low systolic ejection frac ons which have been observed in patients th myocardial disease. Previous studies Grant, Greene and Bunnell[22] and from is laboratory[23] have also demonstrated w stroke work values relative to EDV in atients with myocardial disease Similarly eak power when analyzed with respect to DV provides information relative to the nctional status of the myocardium.

The normalized peak power value may be better index of myocardial performance an the ejection fraction. On the basis of he present data, while there is a fair corre-ation (r = 0.73) between the two indices f function, there is a difference between hese two indices. There is currently no way o decide which is the better measure of myocardial performance. Because the cal culated power includes not only the volume change but also pressure and rate of vol ume change peak power may well provide better measure of myocardial perfor mance than systolic ejection fraction per se.

One patient (No. 38) with the recent onset of hypertension from renal vascular disease had a depressed ejection fraction despite an elevated normalized peak power value. Under these circumstances of the acute increase in impedance to ejection the ejection fraction may not accurately depict ventricular performance. In this patient ventricular peak power was not depressed relative to EDV Thus suggests that under these circumstances ventricular power which incorporates an expression of impedance, may more accurately reflect ventricular performance. However in this study no evaluation was made regarding the responsiveness of peak power values to changes, either acute or chronic, in ven tricular afterload Thus, excessive diuresis was avoided prior to catheterization. Peak power values with respect to EDV and left ventricular mass were studied only in the resting state. Peak power shares the poten tial shortcoming for assessing contractile performance as cardiac output, stroke vol ume and stroke work in that variations in afterload are not taken into account. An other factor which might influence peak power values is the asynergy of contraction of ischemic heart disease but this was not quantitated

A mechanism present in chronic heart disease which is not present in acute studies is ventricular hypertrophy As shown in Fig 7 peak power values normalized for left ventricular mass correlate as well with ejection fraction as do these values normal ized for end-diastolic volume (Fig 6) Numerous investigators have speculated on the stimulus to ventricular dilatation and hypertrophy as a compensatory mech-anism in patients with chronic heart dis-ease. [4,27] Chronic cardiac dilatation and muscular hypertrophy occur concomitantly except in hearts subjected to chronic pres-sure loads, and under these conditions hypertrophy alone may occur[14] Under these conditions peak power or stroke work normalized for ventricular mass may pro-vide a better index of myocardial perfor mance than these parameters normalized for EDV Depressed myocardial perfor mance in chronic heart disease is charac terized by depressed peak power relative to left ventricular mass as well as EDV

We are appreciative of the secretarial assistance of Mrs. Judith Perkins.

REFERENCES

1. Chapman, C. B., Baker O., and Mitchell, J. H. Left ventricular function t rest and during exercise, J Clin. Invest. 38 1202, 1959
2. Bunnell, I. L., Grant, C., and Greene, D G. The measurement of left ventricular power and wall tension in man, Physiologist 5:115 1962.
3. Hernandez, R. R., Greenfield, J C., J and McCall, B. W Pressure-flow studies in hyper-trophic subaortic stenosis, J Clin. Invest. 43:401 1964.
4. Greenfield, J C., J Harley A., Thompson, H. K., and Wallace, A. G., Pressure-flow studies in man during trial fibrillation, J Clin. Invest. 47:2411 1968.
5. Snell, R. E., and Luchsinger P C. Determination of the external ork and power of the left entricle in intact man, Amer. Heart J 69:529 1965.
6. Reeves, T J Hefner L. L., Jones, W B Coghlan, C., Prieto, G., and Carroll, J The hemodynamic determinants of the rate of

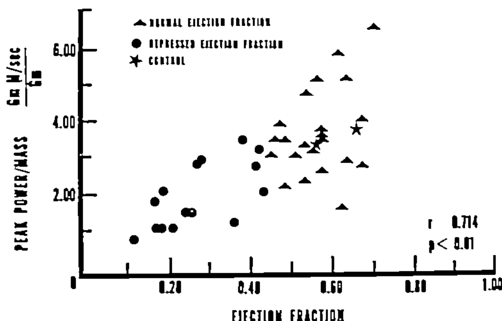


Fig 7 Peak power/mass as a function of the ejection fraction. The linear correlation coefficient of peak power/mass with ejection fraction is = 0 71 ($p < 0.01$)

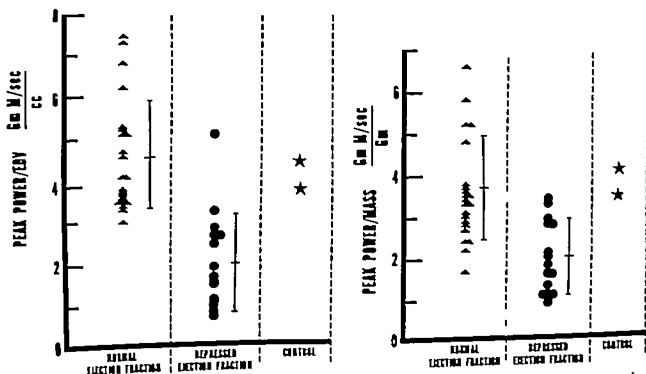


Fig 8 Bar graph of peak power/EDV and peak power/mass for patients with a normal ejection fraction, for those with a depressed ejection fraction, and for the control patients Note the better separation of patients by these ratios than by peak power alone (Fig 2)

Swan[14] the left ventricular ejection fraction was demonstrated to correlate well with peak dp/dt over a wide range The value of dp/dt has been shown by other investigators to provide a measure of ventricular contractility and changes in contractility [7,23] In addition Hood Rackley and Rolett[24] demonstrated that patients with a low ejection fraction have a reduced velocity of contractile element shortening measured at the time of peak wall stress.[3]

Peak power varies widely in patients with heart disease but these values, per se, may give little information concerning the functional status of the myocardium Sarnoff[25] in acute studies in experimental animals,

described myocardial function in terms of *families of curves*.[7] Depressed myocardial function was characterized by low stroke work relative to end-diastolic pressure and accordingly volume. Earlier Patterson Piper and Starling[23] had demonstrated low stroke volumes relative to EDV with myocardial depression in acute studies. This is analogous to the low systolic ejection fractions which have been observed in patients with myocardial disease. Previous studies by Grant, Greene, and Bunnell[17] and from this laboratory[18] have also demonstrated low stroke work values relative to EDV in patients with myocardial disease. Similarly peak power when analyzed with respect to EDV provides information relative to the functional status of the myocardium.

The normalized peak power value may be a better index of myocardial performance than the ejection fraction. On the basis of the present data, while there is a fair correlation ($r = 0.73$) between the two indices of function there is a difference between these two indices. There is currently no way to decide which is the better measure of myocardial performance. Because the calculated power includes not only the volume change but also pressure and rate of volume change peak power may well provide a better measure of myocardial performance than systolic ejection fraction per se.

One patient (No. 38) with the recent onset of hypertension from renal vascular disease had a depressed ejection fraction despite an elevated normalized peak power value. Under these circumstances of the acute increase in impedance to ejection the ejection fraction may not accurately depict ventricular performance. In this patient ventricular peak power was not depressed relative to EDV. This suggests that under these circumstances ventricular power which incorporates an expression of impedance may more accurately reflect ventricular performance. However in this study no evaluation was made regarding the responsiveness of peak power values to changes, either acute or chronic, in ventricular afterload. Thus, excessive diuresis was avoided prior to catheterization. Peak power values with respect to EDV and left ventricular mass were studied only in the resting state. Peak power shares the potential shortcoming for assessing contractile performance as cardiac output, stroke volume, and stroke work in that variations in afterload are not taken into account. Another factor which might influence peak power values is the asynergy of contraction of ischemic heart disease, but this was not quantitated.

A mechanism present in chronic heart disease which is not present in acute studies is ventricular hypertrophy. As shown in Fig. 7 peak power values normalized for left ventricular mass correlate as well with ejection fraction as do these values normalized for end-diastolic volume (Fig. 6). Numerous investigators have speculated on the stimulus to ventricular dilatation and hypertrophy as a compensatory mechanism in patients with chronic heart disease.[17,24,25] Chronic cardiac dilatation and muscular hypertrophy occur concomitantly except in hearts subjected to chronic pressure loads, and under these conditions hypertrophy alone may occur.[26] Under these conditions peak power or stroke work normalized for ventricular mass may provide a better index of myocardial performance than these parameters normalized for EDV. Depressed myocardial performance in chronic heart disease is characterized by depressed peak power relative to left ventricular mass as well as EDV.

We are appreciative of the secretarial assistance of Mrs. Judith Perkins.

REFERENCES

1. Chapman, C. B., Baker, O., and Mitchell, J. H.: Left ventricular function at rest and during exercise, J. Clin. Invest. 38:1202, 1959.
2. Bunnell, I. L., Grant, C., and Greene, D. G.: The measurement of left ventricular power and wall tension in man, Physiologist 3:115, 1961.
3. Hernandez, R. R., Greenfield, J. C., Jr., and McCall, B. W.: Pressure-flow studies in hypertrophic subaortic stenosis, J. Clin. Invest. 43:401, 1964.
4. Greenfield, J. C., Jr., Harley, A., Thompson, H. K., and Wallace, A. G.: Pressure-flow studies in man during atrial fibrillation, J. Clin. Invest. 47:2411, 1968.
5. Snell, R. E., and Luchsinger, P. C.: Determination of the external work and power of the left ventricle in intact man, Amer. Heart J. 69:529, 1965.
6. Reeves, T. J., Hefner, L. L., Jones, W. B., Coghlan, C., Prieto, G., and Carroll, J.: The hemodynamic determinants of the rate of

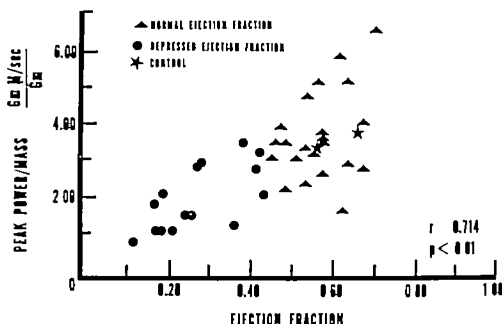


Fig 7 Peak power/mass as a function of the ejection fraction The linear correlation coefficient of peak power/mass with ejection fraction $r = 0.71$ ($p < 0.01$)

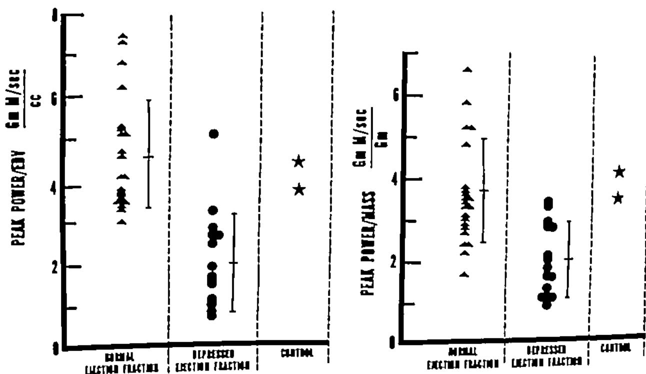


Fig 8 Bar graph of peak power/EDV and peak power/mass for patients with a normal ejection fraction, for those with a depressed ejection fraction, and for the control patients. Note the better separation of patients by these ratios than by peak power alone (Fig 2)

Swan[14] the left ventricular ejection fraction was demonstrated to correlate well with peak dp/dt over a wide range. The value of dp/dt has been shown by other investigators to provide a measure of ventricular contractility and changes in contractility.[7,23] In addition Hood Rackley and Rolett[24] demonstrated that patients with a low ejection fraction have a reduced velocity of contractile element shortening measured at the time of peak wall stress.[14]

Peak power varies widely in patients with heart disease but these values, per se may give little information concerning the functional status of the myocardium. Sarnoff[25] in acute studies in experimental animals,

Case reports

Auscultatory and phonocardiographic sign of ball variance in a mitral prosthetic valve

Joseph Schlager M.D
Edgar P Mannix Jr M.D
Robert E. Wolf M.D **
Brooklyn and Roslyn, N Y

Mitral ball-cage prosthetic valves produce short, loud, and high frequency closure or closing clicks (CC's) and opening sounds or clicks (OC's) which can sometimes be heard unaided several feet from the patient. The normal time interval from aortic valve closure to the opening click (II -OC interval) of the mitral prosthetic valve in patients with Starr Edwards mitral valve prostheses has been reported by Zitnik and Burchell to be 0.08 to 0.15 sec. by Hultgren and Hubis[2] to be 0.07 to 0.15 sec. by Najmi and Segal[3] to be 0.09 to 0.15 sec., and by Boicourt and associates[4] to be 0.06 to 0.13 sec.

Craige[5] has reported that in preoperative patients with mitral stenosis and atrial fibrillation as the R R interval increases (lengthening the diastolic filling period) the left atrium has more time to decompress and the left atrial to left ventricular pressure gradient decreases. During the following cardiac cycle, the opening snap occurs further from the aortic component of the second heart sound (lengthened II -OS interval) Zitnik and Burchell[1] and Najmi and Segal[3] have indicated that this same relationship holds for Starr Edwards mitral valve prostheses, but Hultgren and Hubis[2] reported that only in 4 of 19 patients with atrial fibrillation and mitral valve prostheses was the expected variation in the II -OC interval related to the preceding R R interval.

The present report describes a patient with a Smeloff-Cutter mitral valve prosthesis (First Clinical Model) who had regular sinus rhythm and had intermittent progressive lengthening of the II -OC interval attributable to ball variance of the silicone rubber poppet.

Case report

A 31-year-old postman had replacement of the mitral valve on Aug. 30, 1966, by a Smeloff-Cutter prosthetic valve (First Clinical Model) because of severe, calcific mitral stenosis. Postoperatively the patient was anticoagulated with warfarin sodium. He had an uneventful recovery returned to full-time employment in December 1966, and was well until Oct. 8, 1968, when he complained of transient episodes of aphasia, numbness, and weak

From the Cardiac Catheterization Laboratory The Long Island College Hospital, Brooklyn, N. Y and The Department of Surgery of St. Francis Hospital, Roslyn, N. Y.
Received for publication April 6, 1970.
Reprint requests to: Dr. Joseph Schlager, Cardiac Catheterization Laboratory The Long Island College Hospital, 340 Henry St., Brooklyn, N. Y 11201.
*Director, Cardiac Catheterization Laboratory; Attending Physician, The Long Island College Hospital, Brooklyn, N. Y
**Chief Surgeon and Attending Physician, St. Francis Hospital, Roslyn, N. Y
***Fellow, Cardiac Catheterization Laboratory; Assistant Attending Physician, The Long Island College Hospital, Brooklyn, N. Y

change in pressure in the left ventricle during isometric contraction, AMER. HEART J 60:745 1960.
7. Gleason, W L. and Braunwald E. Studies on the first derivative of the ventricular pressure pulse in man, J Clin. Invest. 41:80 1962.
8. Sonnenblick, E. H Implications of muscle mechanics in the heart, Fed. Proc. 21:975 1962.
9. Sonnenblick, E. H., and Downing S. E. After load as a primary determinant of ventricular performance, Amer J Physiol. 204:604 1963
10. Mitchell J H., Wallace, A. G and Skinner N S. Jr Intrinsic effects of heart rate on left ventricular performance, Amer J Physiol. 205:41 1963
11. Dodge, H T Sandler H. Ballew D W., and Lord J D Jr The use of biplane angiocardiography for the measurements of left ventricular volume in man, AMER. HEART J 60:762 1960.
12. Dodge, H T Sandler H Baxley W A and Hawley R. R. Usefulness and limitations of radiographic methods for determining left ventricular volume, Amer J Cardiol. 18:10, 1966.
13. Dodge, H. T and Baxley W A. Left ventricular volume and mass and their significance in heart disease Amer J Cardiol. 23:528, 1969
14. Miller G. A. H Kirklin J W and Swan H J C. Myocardial function and left ventricular volumes in acquired valvular insufficiency Circulation 31:374 1965
15. Dodge, H. T., and Baxley W A. Hemodynamic aspects of heart failure, Amer J Cardiol. 22:24, 1968.
16. Feigenbaum H Campbell R. W., Wunsch, C. M., and Steinmetz, E. F Evaluation of the left ventricle in patients with mitral stenosis, *Circulation 31:462 1966.*
17. Hood, W P Jr Rackley C. E. and Rolett, E. L.: Wall stress in the normal and hypertrophied human left ventricle, Amer J Cardiol 22:550 1968.
18. Stead E. A. Jr., Warren, J V., and Brannon, E. S Cardiac output in congestive heart failure, AMER. HEART J 35:529 1948.
19. Bunnell I L., Grant, C. and Greene, D G. Left ventricular function derived from the pressure-volume diagram, Amer J Med. 39:881 1965
20. Bartle, S. H. Sanmarco, M E. and Dammann, J F Jr Ejected fraction An index of myocardial function Amer J Cardiol. 15:125 1965.
21. Dodge, H T: Functional characteristics of the left ventricle in heart disease, Ann. Intern. Med. 69:941 1968.
22. Miller G. A. H. Rahimtoola, S. H. Ongley P A. and Swan H J C. Left ventricular volume and volume change in endocardial fibroelastosis, Amer J Cardiol 15:631 1965.
23. Mason D T Usefulness and limitations of the rate of rise of intraventricular pressure (dp/dt) in the evaluation of myocardial contractility in man, Amer J Cardiol 23:516, 1969
24. Hood, W P Jr., Rackley C. E. and Rolett, E. L. Ejection velocity and ejection fraction as indices of ventricular contractility in man Circulation 38:101 1968.
25. Sarnoff S. J Myocardial contractility as described by ventricular function curves. Observations on Starling's law of the heart, Physiol. Rev 35:107 1955
26. Patterson S. W., Piper H., and Starling, E. H. The regulation of the heart beat, J Physiol. 48:465 1914.
27. Grant, C. Greene, D G. and Bunnell I L. Left ventricular enlargement and hypertrophy A clinical and angiocardiographic study Amer J Med. 39:895 1965.
28. Linzbach, A. J Heart failure from the point of view of quantitative anatomy Amer J Cardiol. 5:370, 1960.
29. Harrison, T R. and Reeves, T J Principles *and problems of* ischemic heart disease, Chicago, 1968, Year Book Medical Publishers, Inc., p. 351

Case reports

Auscultatory and phonocardiographic sign of ball variance in a mitral prosthetic valve

*Joseph Schluger M.D.**
*Edgar P. Mannix Jr. M.D.***
*Robert E. Wolf M.D.****
Brooklyn and Roslyn, N. Y.

Mitral ball-cage prosthetic valves produce short, loud, and high frequency closure or closing clicks (CC's) and opening sounds or clicks (OC's) which can sometimes be heard unaided several feet from the patient. The normal time interval from aortic valve closure to the opening click (II -OC interval) of the mitral prosthetic valve in patients with Starr Edwards mitral valve prostheses has been reported by Zitnik and Burchell[1] to be 0.08 to 0.15 sec. by Hultgren and Hubis[2] to be 0.07 to 0.15 sec., by Najmi and Segal[3] to be 0.09 to 0.15 sec. and by Boscourt and associates[4] to be 0.06 to 0.13 sec.

Craige[5] has reported that in preoperative patients with *mitral stenosis* and *atrial* fibrillation as the R R interval increases (lengthening the diastolic filling period), the left atrium has more time to decompress and the left atrial to left ventricular pressure gradient decreases. During the following cardiac cycle, the opening snap occurs further from the aortic component of the second heart sound (lengthened II -OS interval). Zitnik and Burchell[1] and Najmi and Segal[3] have indicated that this same relationship holds for Starr Edwards mitral valve prostheses, but Hultgren and Hubis[2] reported that only in 4 of 19 patients with atrial fibrillation and mitral valve prostheses was the expected variation in the II -OC interval related to the preceding R R interval.

The present report describes a patient with a Smeloff-Cutter mitral valve prosthesis (First Clinical Model) who had regular sinus rhythm and had intermittent, progressive lengthening of the II -OC interval attributable to ball variance of the silicone rubber poppet.

Case report

A 31-year-old postman had replacement of the mitral valve on Aug. 30, 1966, by a Smeloff-Cutter prosthetic valve (First Clinical Model) because of severe, calcific mitral stenosis. Postoperatively the patient was anticoagulated with warfarin sodium. He had an uneventful recovery returned to full-time employment in December 1966, and was well until Oct. 8, 1968, when he complained of *transient* episodes of aphasia, numbness, and weak

From the Cardiac Catheterization Laboratory The Long Island College Hospital, Brooklyn, N. Y. and The Department of Surgery of St. Francis Hospital, Roslyn, N. Y.
Received for publication April 6, 1970.
Reprint requests to: Dr. Joseph Schluger, Cardiac Catheterization Laboratory The Long Island College Hospital, 340 Henry St., Brooklyn, N. Y. 11201.
*Director, Cardiac Catheterization Laboratory; Attending Physician, The Long Island College Hospital, Brooklyn, N. Y.
**Chief Surgeon and Attending Physician, St. Francis Hospital, Roslyn, N. Y.
***Staff, Cardiac Catheterization Laboratory Assistant Attending Physician, The Long Island College Hospital, Brooklyn, N. Y.

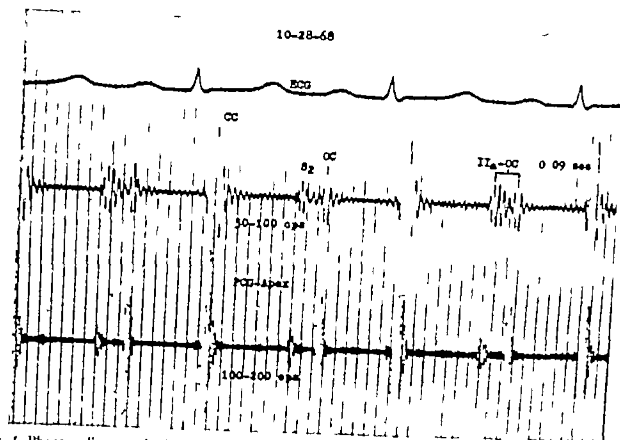


Fig *1* Phonocardiogram obtained Oct. 28 1968 at the cardiac apex. The patient was supine and held his breath at the end-expiratory phase of respiration *CC* = Closing click of the mitral prosthetic valve *OC* = opening click of the mitral prosthetic valve *S* = second heart sound. The II -OC interval was con tant at 0.09 sec. (Paper speed 100 mm. per second and time lines of 0 04 sec.)

ness of the right hand. The ymptoms would persist for 10 min. and subside completely and spontaneously The patient was hospitalized and continued to have frequent transient episodes of right upper extremity weakness and aphasia, even though the prothrombin time was within the therapeutic range Physical examination revealed slightly hyperactive deep tendon reflexes in the right upper limb and intermittent partial expressive aphasia The closing and opening sounds of the m tr l valve prosthesis were present and the II -OC i terval was constant. He was treated with a continuous infusion of i tra venous heparin (300 mg daily) and all symptoms and signs subsided within several days.

Phonocardiography was performed on Oct 28, 1968 using an Electronics for Medicine DR-8 Recorder with a multiple band phono-amplifier (Model TPD) and a PS-1B microphone Band widths were 50 to 100 and 100 to 200 c p.s. and the patient was in the supine position. A loud CC and OC were recorded and the II -OC interv l was constant at 0.09 sec (Fig. 1) The patient cardiac rhythm was regular at 88 beats per minute

Following this hospitalization the patient was well and again returned to full time employme t During a routine monthly examination on April 30 1969 an unusual change in the rhythm of the prosthetic sounds was noted. By auscultation it seemed that an arrhythmia was present but simultaneous electrocardiography and auscultation revealed that there was, in fact, no arrhythmia. Phonocardiography was performed on May 1 1969 with the patient in the supine and sitt ng positions which demonstrated that the change in the auscultatory findings was d e to a variable delay in the II -OC interval from 0 09 up to 0.25 sec. (Figs. 2 and 3) The delay in the II -OC interval occurred intermittently and mostly in the sitting position. The longer the II -OC i terval the greater the amplitude of the OC. Cardiac rhythm was regular and the ate varied from 88 to 100 beats per minute. Image ntensification fluoroscopy and cineroent genography showed faint opacification of the silicone rubber poppet and a intermittent change in the normal rhythmic motion of the cage which coincided with the delay in the OC. The cha ge in rhythm was due to an intermittent delay in open ng of the mitral prosthetic alve followed by a more forceful descent of the ball into the ventricular cage which imparted syncopated effect to the rhythmic motion of the prosthetic valve.

The patient cont nued to feel perfectly well and rema ned at work without difficulty Phonocardiography was perforn ed on M y 16, 1969 while the patient was supine, sitt g and inclined t 45 degrees. The delays n the OC were considerably more frequent when the patient was sitting or inclined at 45 degrees and almost disappeared when the patient was supine. The ange of the II -OC terval was from 0 09 to 0.31 sec. (F g 4) Cardiac rate was essentially unchanged from the previous rates.

On each revisit, the delays in the OC occurred

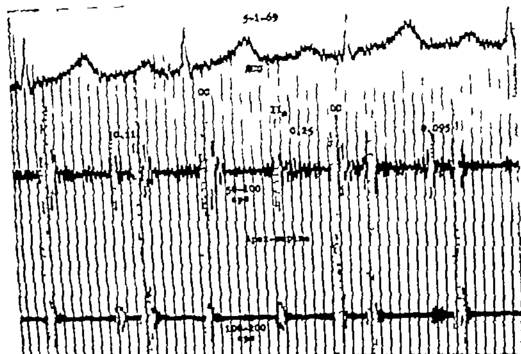


Fig. 2. Phonocardiograms obtained May 1, 1969 at the cardiac apex with the patient holding his breath at the end-expiratory phase of respiration while supine. The numbers represent the duration of the variable II_A-OC intervals.



Fig. 3. Phonocardiograms obtained May 1, 1969 at the cardiac apex with the patient holding his breath at the end-expiratory phase of respiration while sitting. The numbers represent the duration of the variable II_A-OC intervals.

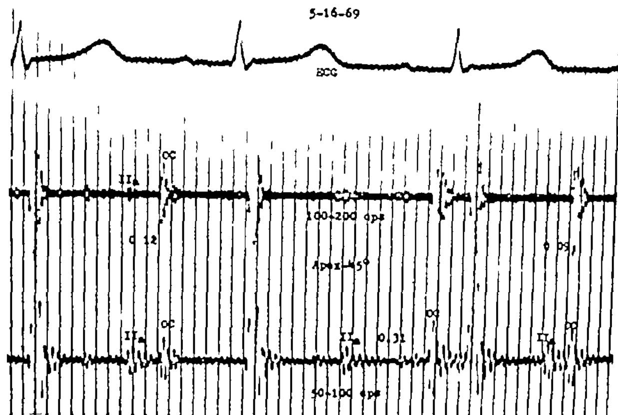


Fig 4 Phonocardiogram obtained May 16 1969 at the cardiac apex with the patient's torso elevated to 45 degrees. The II -OC interval varied from 0 09 to 0 31 sec

more frequently and became progressively more prolonged in duration. Phonocardiography was again performed on June 25 1969 The range of the II -OC interval was from 0 09 to 0 36 sec. (Fig 5) The cardiac rate was 79 beats per minute and the rhythm was regular Because of the progressive increase in the II -OC interval and the possibility that the poppet might become permanently lodged in the cage in the closed position leading to sudden death, reoperation was advised.

On July 2, 1969 reoperation was performed and the Smeloff-Cutter (First Clinical Model) mitral valve prosthesis was replaced by a Beall disc prosthesis. At operation a 2 mm by 4 mm thrombus was present at the base of one of the struts of the atrial cage. Fine strands of fibrotic material were noted at two other sites in the ring material of the prosthesis. The ball appeared stained yellow but was otherwise intact. When the removed prosthetic valve was held with its atrial cage upward the ball fell into the ventricular cage and rested on the struts (Fig 6 A) When the prosthetic valve was inverted so that the atrial cage was dependent, the ball fell into the atrial cage but there was a small space between the ball and the struts (Fig 6 B) When the ball was manually pushed further into the atrial cage, it would not fall back into the ventricular cage when the prosthetic valve was reinverted.

The patient's condition on the first postoperative day was satisfactory but he developed progressive dyspnea and tachypnea on the second day Chest roentgenograms showed bilateral parenchymal infiltrates which rapidly became more extensive. Despite intensive therapy including massive doses of corticosteroids, the patient died on the third postoperative day Permission for autopsy was denied.

Discussion

Alterations in physicochemical properties of the silicone rubber poppet of a ball-cage valve prosthesis causing variations in its size or shape following implantation can have serious hemodynamic consequences which may ultimately cause death of the patient [4, 10] Laforet[4] suggested that muffling of the characteristic clicking imparted by a well functioning poppet may prove to be a valuable auscultatory sign of ball variance in the aortic prosthetic valve. Herr and associates[9] stated that the loss of the prosthetic ejection click upon auscultation and phonocardiography is diagnostic of aortic valve ball variance. Phonocardiography has been shown by Hylen and co-workers[11] to be useful in detecting aortic ball variance in Starr Edwards aortic valve prosthesis Model 1000 series. These investigators compared the amplitude of the aortic

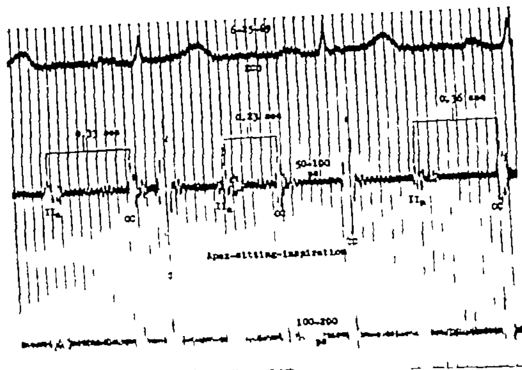


Fig. 5 Phonocardiogram obtained June 25 1969 at the cardiac apex while the patient was sitting and holding his breath at the end-inspiratory phase of resperation. The II -OC interval varied to maximum of 0.36 sec.

opening sound (AO) to the aortic closure sound (AC) recorded over the second right intercostal space. The AO/AC ratio was less than 0.5 in 10 of 12 patients with confirmed aortic ball variance. Only one patient with an AO/AC ratio less than 0.5 was not found to have ball variance at reoperation but in this patient, with a Model 1200 series valve, clot extending over the cage struts probably caused the diminished AO Loss of the characteristic high spiking frequencies of both aortic opening and aortic closure sounds was present in two patients with confirmed aortic ball variance. Neither a variation in the intensity of the AO from one cycle to another nor the measurement of a variety of time intervals was found to be useful in detecting aortic ball variance because of the overlap between normal" and abnormal valves. At present Hylen and associates[11] consider an AO/AC ratio of less than 0.5 obtained on at least two occasions diagnostic of ball variance. Patients with AO/AC ratios in the range of 0.5 to 0 7 are followed closely for further evidence of ball variance. The complete absence of the AO is an urgent indication for reoperation.

Hylen and co-workers[11] state that the *presence of atrial fibrillation makes the* detection of changes in the AO by auscultation most difficult because of marked variation in the sounds with changing R R intervals. This problem can be obviated by averaging AO amplitudes as re*corded on the phonocardiogram* and excluding those that follow R R intervals less than 0.5 sec. The same authors[11] state that patients with ball variance of aortic prosthetic valves have an opening sound of lower frequency (as well as lower amplitude) so that the opening sound is more like a thud rather than a click. The loss of the high-frequency components of the AO is a characteristic of ball variance and has been documented by sound spectrograms.

In the diagnosis of ball variance of mitral prosthetic valves, the relative amplitude of the opening and closing clicks has not been found to be useful. Sanderson Hall and Thomas[12] reported a case of ball variance in a SCDK mitral valve pros-

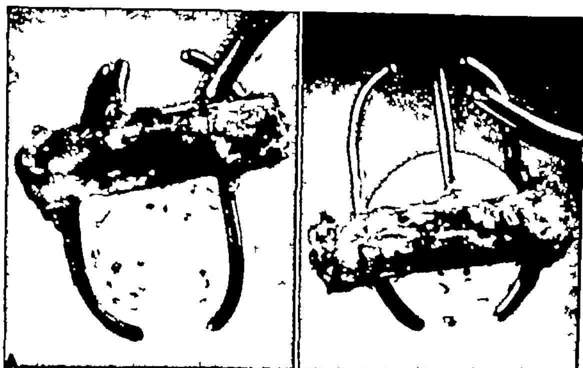


Fig 6 Removed Smeloff Cutter mitral prosthetic valve (First Clinical Model) with ventricular cage dependent (A) and with atrial cage dependent (B) See explanation in text.

thesis that had a varying time interval from aortic closure to the opening click The II -OC interval varied from 0 10 to 0 62 sec Leatherman and associates[14] reported two more cases of ball variance in No 825 Cutter mitral prostheses associated with erratic opening sounds varying arterial pulse pressure and sinus rhythm The phonocardiogram published showed either a delay in the II -OC interval or the absence of the opening click in some cycles Smeloff and McHenry[15] have also reported two patients with SCDK mitral valve prostheses in whom phonocardiographic evidence of an increased II -OC interval indicated the occurrence of ball variance In the experience of these authors the II OC interval in patients with a SCDK mitral prosthesis should not exceed 0 15 sec In the case reported herein there was a progressive lengthening of the II -OC interval to 0 36 sec over a period of six weeks beginning 32 months following insertion of the mitral valve prosthesis Occasionally complete absence of the mitral opening click is noted intermittently in a cardiac cycle[14,15] in mitral prosthesis ball variance Continuous absence of the opening sound on the other hand has been noted in massive thrombosis of a mitral prosthesis[16] as well as in dehiscence of a mitral valve prosthesis.[17] A muffled and almost inaudible opening sound and a systolic murmur was reported in a case of ball variance in a Starr Edwards prosthetic mitral valve by Connolly Harrison and Ellis.[18] Craige Hutchin and Sutton[19] reported a delay in the aortic closure sound to the mitral opening sound interval in a Starr Edwards mitral prosthesis (6300 series) in a patient with both aortic and mitral prostheses due to thrombus formation on the annulus of the prosthesis.

In addition to the two cases reported by Smeloff and McHenry[15] 10 additional cases of swelling of the mitral prosthetic ball with subsequent sticking have been reported by Cutter Laboratories, Inc.[20] The ball variance reported by this manufacturer has been shown to be due to plasma lipid absorption by the silicone rubber poppet[20,21] and is believed to be related to the severe heat treatment used in curing the poppet Since September 1966 a milder heat treatment has been employed in curing the poppets and no cases of mitral prosthetic ball variance have been reported with this model (Smeloff Cutter Present Clinical Model) It

must be pointed out that although two cases[14] of ball variance occurred at 8 and 10 months following insertion of No. 825 Cutter mitral prostheses, the two patients[13] with SCDK mitral prostheses and the patient with a Starr-Edwards mitral prostheses developed phonocardiographic evidence of ball variance as late as 37, 48, and 50 months following insertion. In the present case, the earliest ausculta tory abnormal ties did not occur *until* 32 months *following* insertion of the prosthetic mitral valve.

In addition to the case of ball variance with phonocardiographic abnormalities in a Starr-Edwards mitral prosthesis reported by Connolly, *Harrison* and Ellis, six additional cases of Starr-Edwards mitral prostheses had documented ball variance.[13]

Despite continued progress in the development and manufacture of prosthetic valves, *thousands of patients* have had prosthetic valves implanted that are no longer in use because of subsequent modifications and improvements. Since ball variance does not usually occur for many *months or years following insertion* it is necessary to obtain periodic phonocardiograms. Careful serial measurements should be made of the various phonocardiographic parameters suggestive of ball variance. At present, phonocardiography permits the earliest possible diagnosis of ball variance and allows for reoperation with avoidance of sudden catastrophic and fatal events. The appearance of symptoms suggestive of ball variance (late onset of fatigue congestive heart failure dyspnea palpitation, arrhythmia, dizzy spells syncope, hemolytic anemia, jaundice hemoglobinuria or angina [11]) indicate that a phonocardiogram should be obtained for analysis. Even though the early diagnosis of ball variance is now possible in some patients, reoperation entails major surgery which in itself may have a fatal outcome. The reported operative mortality rate for patients with suspected aortic ball variance has been 12.8 per cent (5 of 39 patients) [12]

Summary

Progressive lengthening of the II -OC interval in a patient with a Smeloff-Cutter (First Clinical Model) mitral valve prosthesis is reported This event occurred 32 months following insertion of the valve and was indicative of *malfunction of the* prosthetic valve due to ball variance. The reported experience relating to the auscultatory and phonocardiographic diag nosis of ball variance in ball-cage prosthetic valves with silicone rubber poppets is reviewed

REFERENCES

1. Zitnik, R. S., and Burchell, H. B. A phonocardiographic study of patients with total prosthetic mitral al replacement, Dis. Chest 44 11 1963.
2. Hultgren, H N and Hubis, H. A phonocardiographic study of patients with the Starr Edwards mitral valv prosthesis, AMER. HEART J 69:309 1965
3. Najmi, M., and Segal, B. L. Auscultatory and phonocardiographic findings in patients with prosthetic ball-valves, Amer J Cardiol. 16 794 1965.
4. Boncourt, O W Bristow J D Starr A., and Griswold, H. E. A phonocardiographic study of patients with multiple Starr-Ed ard prosthetic val es, Brit. Heart J 28:531 1966.
5. Craige, E. Phonocardiographic studies in mitral stenosis, New Eng. J Med. 257:650, 1957
6. Laforet, E. G Death due to swelling of ball component of aortic ball-val e prosthesis, New Eng. J Med. 276 1025 1966.
7. Magovern, G. J.: Discussion (G. J Magovern, E. M. Kent, and W B Cushing Sutureless mitral valv replacement), Ann. Thorac. Surg. 2:474, 1966.
8. Cooley D. A., Blood ell, R. D Beall, A. C., J Gill, S. S., and Hallman, G. L. T tal cardiac alve replacement using SCDK-Cutter prosthesis: Experience with 250 consecutive patients, Ann. Surg. 164:428, 1966.
9. Herr R. H., Kloster F E Sessi, Y and Starr A. Diagnosis and management of "ball variance following aortic valv replacement, *Circulation* 36(Suppl. II) 141 1967
10. Roberts, W C., and Morrow A. G. Fatal degeneration of the silicone rubber ball of the Starr Edwards prosthetic aortic val e, Amer J Cardiol. 22:614 1968.
11. Hylen, J C., Kloster F E., Herr R. H Hull, P Q Ames, A. W Starr A., and Griswold, H. E. Phonocardiographic diagnosis of aortic ball variance, Circulation 38:90 1968.
12. Hylen, J C., Kloster F E., Starr A., and Griswold, H. E Aortic ball ariance: Diagnosis and treatment, Ann. I tern. Med. 72 1 1970.
13. Sanderson, R. G., Hall, A. D and Thomas, A. N The clinical diagnosis of ball ariance in mitral valve prosthesis, Ann. Thorac. Surg. 6:473, 1968.

14 Leatherman, L. L. Leachman, R. D McCoon, R. G Hallman, G L. and Cooley D A. Malfunction of mitral ball-valve prostheses due to swollen poppet J Thorac. Cardiovasc. Surg 57:160, 1969
15 Smeloff E. A. and McHenry M M Ball variance—experience as reported by E. A. Smeloff M D Human prosthetics, Progress report 2 1969 Cutter Laboratories, Inc. pp 3-6.
16. Spencer F C. Trinkle, J K. and Reeves, J T Successful replacement of thrombosed mitral ball valve prosthesis, J.A.M.A. 191:1249 1965
17 Leachman R. D and Cokkinos, D V P Absence of opening click in dehiscence of mitral-valve prosthesis, New Eng J Med 281:461 1969
18. Connolly D C. Harrison C. E., Jr and Ellis, F H Jr Ball variance in a Starr Edwards prosthetic mitral valve causing acute pulmonary edema (diagnosis by auscultation before onset of symptoms) Mayo Clin. Proc. 45:20 1970
19 Craige E. Hutchin, P and Sutton, R. Impaired function of cloth-covered Starr Edwards mitral valve prosthesis, Circulation 41:141 1970.
20. Kahn, P and Carmen, R. A.: Ball variance—total experience. Human prosthetics, Progress report 2 1969 Cutter Laboratories, Inc., pp. 1 2.
21 Carmen R. A. and Kahn P In vitro testing of silicone rubber heart valve poppets for lipid absorption, J Biomed Mat. Res. 457 1968.

T wave alternans: An association with abrupt rate change

Charles Fisch, M.D.
Robert E. Edmands, M.D.
Kalman Greenspan, Ph.D.
Indianapolis, Ind.

Although alternation in polarity of the T wave without any demonstrable change in the QRS ("isolated alternans) was recorded from a cat papillary muscle by Taussig as early as 1928,[1] it was not until 1969 that a clinical example of this entity was reported by Ricketts, Denison, and Haywood[2] in a patient with alcoholic cardiomyopathy. An instance of isolated T wave alternans but without actual reversal of polarity was described earlier by Kimura and Yoshida in a patient following cardiovascular collapse.

It is the purpose of this communication to present a case of isolated T wave alternans with reversal of polarity and to point out that the alternans, although occurring independently of any demonstrable change in the QRS, was affected markedly by relatively minor changes in the heart rate.

Case report

The patient, an 80-year-old man, was admitted because of symptoms of urinary tract infection secondary to benign prostatic hypertrophy.

Physical examination disclosed a blood pressure of 210/120. The heart was enlarged with the point of maximum impulse outside the midclavicular line. It was normal as to rate, rhythm, and sounds. The only other abnormality found on examination was uniform enlargement of the prostate.

While a urinary catheter was anchored in order to determine the residual volume, he suddenly appeared to be in respiratory distress and an ECG revealed ventricular fibrillation. Prompt defibrillation restored normal sinus rhythm. The patient was disoriented, confused, and agitated for some hours. These symptoms cleared gradually. Although hemodynamic studies were not feasible, repeated determinations of blood pressure and palpation of the pulse failed to disclose any evidence suggestive of mechanical alternation. Pulse tracings were not recorded, however.

Laboratory studies performed during hospitalization showed moderate cardiac enlargement on x-ray and repeatedly normal hemoglobin, serum sodium potassium chloride, and pH. The blood urea nitrogen which at time of admission was 50 mg. per cent declined to 24 mg. per cent at time of discharge. The various laboratory tests could not be related temporally with any degree of reliability either to the episode of ventricular fibrillation or the subsequent electrocardiograms (ECG).

Fig. 1 (Sept. 9, 1967) was recorded shortly after termination of ventricular fibrillation and demonstrates sinus rhythm interrupted by atrial prema-

From the Department of Medicine, Indiana University School of Medicine, and the Krannert Institute of Cardiology, Marion County General Hospital, Indianapolis, Ind.

Supported in part by the Herman C. Krannert Fund, United States Public Health Service Grants HE-4308, HTS-5363, and HE-6749, the Indiana Heart Association, and the American Medical Association Committee for Research on Tobacco and Health.

Received for publication April 5, 1 70.

Reprint requests to: Charles Fisch, M.D., Department of Medicine, Indiana University Medical Center, 1 00 West Michigan St., Indianapolis, Ind. 46202.

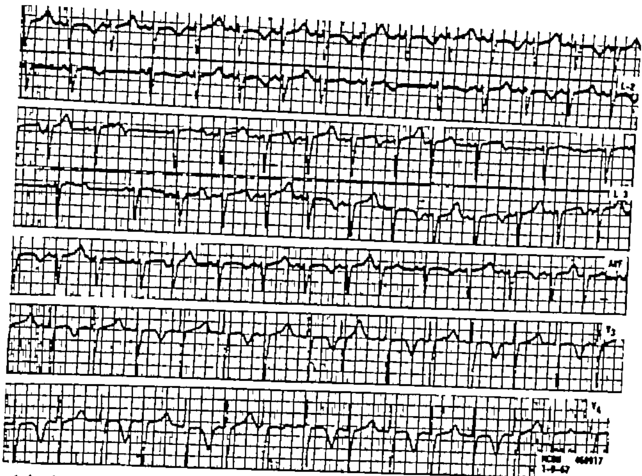


Fig *1* \n electrocardiog,ram recorded shortly after termination of ventricular fibrillation See text for discussion.

ture systoles (APS) some blocked a in Lead II and III and some conducted w th a resultant variation of the R R interval The dominant 1 P interval measures 0 74 second The 1 R interval is normal The QRS s prolonged to 0.12 second with the morphology as best can be determined from the surface ECG remaining consta t for any given lead The Q-T is prolo ged. The T wave alternans with changing polarity is recorded in all leads and appears on the rf ice, over a nun ber of cycles, to be independent of the heart rate. This is best illustrated in \ where the don nant sinus rhythm is interrupted by only one \PS However inspection of the magn tudo of the T waves reveals definite change n both the dep th and height of the T waves following the \PS when compared with those preced ng the APS It is also of interest to note that in the upper strip of Lead III where the ventricular rate is slowed by nonconducted APS's alteration of the T wave which follows the long pause appears negl gible when compared w th the remainder of the lead. In the lower trip of Lead III (continuous) the alternans resu nes with acceleration of the ventricular rate.

Fig 2 (Jan. 1 1967) not only demonstrates the isolated T wave alternans but also over rela tively long periods this alternans appears to be independent of the heart rate, with the sinus rate being regular at a P P interval of 0 68 second

The tracing obtained on Jan. 11 1967 (F'g 2) demonstrates the dependency of the T wave alternans on the preceding cycle length be this cycle prolonged or slightly foreshortened. In \ a blocked APS results n a prolongation of the R R from a basic 0 64 second interval to 1 08 seconds and this is followed by triking postextrasystolic T wave change. Sim larly relatively small degrees of foreshortening of the R R interval, from the basic 0.62 second to 0.58 second (sixth R R in V_4) and to 0.53 second (ninth R R in V_4) are followed by a distinct increase n T wave ampl tude (the more marked R R abbreviation is followed by the more striking T wave increase) In V_4, a nonconducted \PS yields an R R prolongation from 0 68 to 1 04 seconds, followed by a brief alternans of four beats in duration (termination by another \PS)

Fig 3 (Lead \ Is conti uous) was recorded later that same d y and demonstrates the dependency of the lternans on m nor variation of the R R cycle nd the gradual wa ng of the alternans p- pearing after an abrupt cycle length change. The basic R R nterval measures 0.74 second \trial premature systoles (0.66 second i \ and V_4, respecti ely) are followed by "Isolated T w o alternans which gradually becomes less pronounced. The sinoatrial rhythm n \ is terminated by an APS.

O Jan 12 1967 an ECG demonstrated interval-dependent alternation in amplitude of the T wave but an actual hange in polarity was recorded only in Leads V_4, V_5, and V_6 and this as much less pronounced than in the traci g of Sept. 9 1967 An ECG recorded on Jan. 16, 1967 no longer dem onstrated alternation.

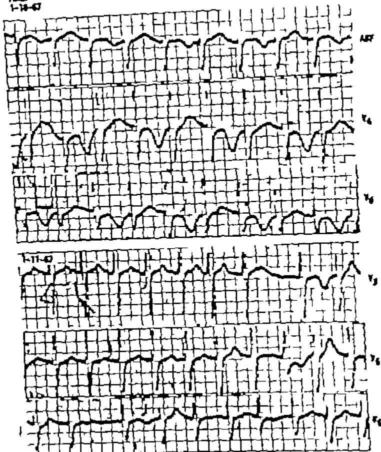


Fig. 2. Electrocardiograms recorded on the succeeding two days. See text for discussion.

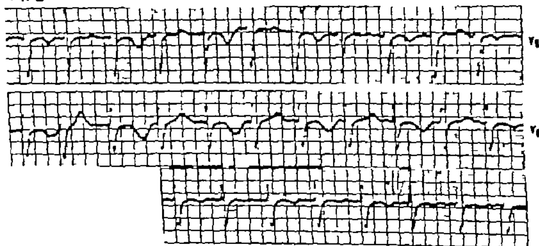


Fig. 3. An electrocardiogram recorded later on the same day as that exhibited in Fig. 2. See text for discussion.

Discussion

This case report exhibits evidence of electrical alternans of repolarization (T wave alternans) that is greatly affected by abrupt rate change. More specifically this was either precipitated or accentuated by abrupt cycle length prolongation either by an APS with a compensatory pause or following the cycle-length prolongation associated with a nonconducted APS Acceleration of the ventricular rate also characteristically evoked T wave alternans. In addition it is apparent from many portions of this record that the electrical alternans is commonly contingent upon the cycle length change per se the T wave alternation is often striking after a premature beat with a compensatory pause gradually dissipating over a variable number of complexes at the regular rate

The assumption that the alternans is isolated or independent of QRS changes is based on inspection of the surface ECG which at best is a rather crude means of estimating electrophysiologic events. Indirect evidence supporting the assumption that the alternans is isolated comes from study of this phenomenon in the single cell using microelectrode techniques.[4,6] But even here until phase 0 of the alternating transmembrane action potential (TAP) is differentiated one cannot be absolutely sure that the alternans of phase 2 and phase 3 (repolarization) of TAP is truly independent of changes of depolarization (phase 0) Assuming that the T wave changes are independent of QRS changes it is in this case influenced to a great extent if not actually dependent on abrupt cycle-length change.

This association of abrupt rate change with primary alternans of the T wave is not an entirely novel observation however In his initial description of the postextrasystolic T wave change White[7] described a brief postextrasystolic alternans of the T wave in about a third of the tracings. Similar transient electrical alternans has been described by others,[8] following premature beats with a compensatory pause. Careful analysis of the patient studied by Kimura and Yoshida[4] reveals a comparable relationship between rate change and electrical alternans. The tracing in the paper by Ricketts Denison and Haywood[3] and that recorded by us on Jan 10 1967 (Fig 2) are probably too brief to exclude this proposed relationship In any case interval-dependent alternation of repolarization is recorded uniformly from single cells of isolated myocardial tissue whether animal[9,10] or human[11]

In clinical settings, with the exception of alternans associated with very rapid heart rates and perhaps minimal postextrasystolic alternation T wave alternans of any magnitude is generally assumed to be indicative of myocardial disease.[4] However alternation of repolarization associated with abrupt rate change is routinely recorded from normal isolated myocardial cells.[9,11] Similarly T wave alternans is recorded in epicardial electrograms in intact dogs while the concomitant surface ECG records no discernible T wave alterations.[12] Furthermore it has been observed that the magnitude of the alternans is increased after myocardial depression by barbiturates and that such alternation perseveres at slower rates in the presence of myocardial depression[12]

Thus evidence is presented that marked alternation of the T wave occurring without discernible change in the QRS configuration is contingent upon abrupt rate change and that it persists at more rapid heart rates, much as in the case of minimal postextrasystolic alternans and the alternans occurring with very rapid heart rates in normal hearts. The distinction it is suggested is more quantitative than qualitative involving the magnitude and persistence of T wave alternans, both of which are exaggerated in the presence of myocardial disease. As noted previously[12] interval-dependent alternans may occur more commonly than is generally conceived the T wave changes may frequently be of insufficient magnitude to be recorded on the surface ECG

The three instances of isolated T wave alternans two with alternation in polarity reported in the literature were all associated with severe myocardial disease. In our case the gradual decrease

in *magnitude of* alternation as the condition of the patient improved and its ultimate total disappearance strongly indicates the dependence of magnitude of alternation on the severity of the underlying condition. Our case also illustrates the fact that unless long records are available the dependency of alternation on abrupt cycle length change may be overlooked.

Summary

A case of alternation of T wave with reversal of polarity independent of any changes of the QRS but apparently greatly influenced by abrupt cycle length change, is presented.

Evidence suggests that this phenomenon is indicative of severe myocardial disturbance.

REFERENCES

1. T mulz, H. B. Electrograms taken *from* isolated strips of mammalian ventricular cardiac muscle, Bull. Hopkins Hosp. 43:81 1928.
2. Ricketts, H. H., Denison, E. K., and Haywood, L. J.. Unusual T-wave abnormality Repolarization alternans associated with hypomagnesemia, acute alcoholism and cardiomyopathy J.A.M.A. 207:365, 1969
3. Kimura, E., and Yoshida, K. A case showing electrical alternans of the *T wave without* change in the QRS *complex*, AMER. HEART J 65:391 1963.
4. Hoffman, B. F and Suckling, E. E. Effect of heart rate on cardiac membrane potentials and the unipolar electrogram, Amer J Physiol. 179 123, 1954.
5. Kleinfeld, M Stein, E. and Kossmann, C. E.: Electrical alternans with emphasis on recent observations made by means of single-cell electrical *recording*, AMER. HEART J 65:495 1963.
6. Kleinfeld, M and Stein, E.: Electrical alternans of components of action potential, AMER. HEART J 75:528, 1968.
7. White, P D Alternation of the pulse. A common clinical condition, Amer J Med. Sci. 150:82 1915.
8. Laubry C., and Pournaillont, M. L Alternance electrique, Arch. Mal. Coeur 23:456, 1930.
9. Edmands, R. E., Greenspan, K., and Fisch, C. Effect of cycle-length alteration upon the configuration of the canine ventricular action potential, Circ. Res. 19:602, 1966.
10. Greenspan, K., Edmands, R. E., and Fisch, C.. Effects of cycle-length alteration on canine cardiac action potentials, Amer J Physiol. 212 1416, 1967
11. Fisch, C., Edmands, R. E., and Greenspan, K.: The effect of change in cycle length on the entricular action potential in man, Amer J Cardiol. 21:525, 1968. (Abst.)
12. Edmands, R. E., Greenspan, K., Lee, D and Fisch, C. The effects of inotropic agents on *the* post-extrasystolic T wave change, Fed. Proc. 27(11) March-April, 1968. (Abst.)

Clinical pathologic conference

Kirkor I. Karachorlu, M.D.
Rolf M. Gunnar, M.D.
Cecil A. Krakower, M.D.
Chicago, Ill.

Case report

Clinical abstract. This was the third admission for this 25-year-old Negro woman to the University of Illinois Neuropsychiatric Institute. She was a gravida V, Para 4, who had been separated from her husband. She was hospitalized twice early in 1968, with a diagnosis of schizophrenia of chronic undifferentiated type. Recently she was rehospitalized at the Chicago State Hospital because of exacerbation of her psychotic symptoms. She was released from there and transferred to this hospital on Sept. 23, 1969. On admission the patient stated that she had had severe headaches, her hair was falling out, and that she felt depressed and confused. She had no previous history referable to diabetes, tuberculosis, carcinoma, renal or cardiac disease, anemia, or hypertension. On the previous admissions she stated that she was allergic to penicillin. However, on this admission, she denied such an allergy. She had been taking birth control pills for 5 years. There was no history of seizures.

Physical examination. Physical examination revealed a thin, depressed young Negro female. Blood pressure was 110/70 mm. Hg, pulse 110 per minute, temperature 97° F., and respiration 24 per minute. The head, eyes, ears, nose, and throat were normal. The chest was symmetrical. The lungs were clear to percussion and auscultation. The cardiovascular system revealed mild tachycardia, regular rhythm, S_1 and S_2 within normal limits, and no S_3, S_4, or murmurs. The point of maximum impulse was at the fifth intercostal space in the midclavicular line. The abdomen was flat, soft, and nontender. No organs or masses were felt. Examination of the nervous system revealed that cranial and major motor nerves were intact. Deep tendon reflexes were hyperactive. There was no clonus. The gait was within normal limits. Coordination was good.

Laboratory data. Blood glucose was 111 mg. per cent, urea 10 mg. per cent, creatinine 1.0 mg. per cent, hematocrit 45 per cent, hemoglobin 14.2 Gm. per 100 c.c., and white blood cell count 12,600 per cubic millimeter with normal differential. The Venereal Disease Research Laboratory test was nonreactive. Urine analysis was negative for sugar, protein, and acetone. The skull and chest x-rays showed no abnormalities.

Hospital course. The patient was treated even as on the previous admissions with Stelazine 5 mg., Navane 5 mg., chloral hydrate 0.5 Gm., and increasing doses of Thorazine up to 600 mg. daily. She was doing quite well during the last week of her hospitalization. Her psychiatrists were considering discharging her. However, on Nov. 24, 1969, the patient complained of vague chest pain. She was examined by a resident physician. No physical defects were found. Darvon 65 mg. was given to relieve the pain. The next day, Nov. 25, 1969, she felt sick, complained of chest pain again, and refused to go to occupational therapy. Her condition worsened and during the night she developed a low-grade fever (101° F.) with cough, sweats, and chills. On Nov. 26, at 9:00 a.m., examination revealed temperature 103° F., blood pressure 110/50 mm. Hg, and labored respirations 40 per minute. The skin was moist and warm. There was slight cyanosis of the lips with pallor. There were decreased breath sounds and resonance over the right lower lobe of the lung. Cardiovascular examination revealed pulse 130 per minute and regular, and apex at the fifth intercostal space. S_1 was maximum at the apex, and S_2 was maximum at the second left intercostal space and split physiologically. There was slight venous distention of the neck veins. Gram stain of the sputum showed gram-positive bacilli. A chest x-ray reported an infiltrate in the right lung. The patient was treated for pneumonia. She was given, intramuscularly, 600,000 units of procaine penicillin and 300,000 units of aqueous penicillin at 10:27 a.m. At 10:29 a.m. (2 min. after injection) the patient

From the College of Medicine and Department of Pathology, University of Illinois Hospital, Chicago, Ill.
Reprint requests to: Cecil A. Krakower, M.D., College of Medicine, Department of Pathology, University of Illinois Medical Center, Chicago, P. O. Box 6998, Chicago, Ill. 60680.

 June, 1971, Vol. 81, No. 6, pp. 822-831

Table I

Time	Location	Systolic pressure (mm. Hg)	Diastolic pressure (mm. Hg)
4.22 p.m.	Left ventricle	91	35
	Aorta (arch)	88	39
4.23 p.m.	Left entricle	98	35
4.23 p.m.	Aorta (at val)	116	58
	Aorta (arch)	116	58

had cardiac arrest. External cardiac massage was begun. Calcium chloride, sodium bicarbonate. Adrenalin, and Levophed, intra enously were given. Oxygen was applied. At 10.35 a.m. the patient blood pressure rose t 75/35 mm. Hg and she was transferred to the cardiac unit. At 11.30 a.m., the patient pulse as eakly palpable. The pupils were dilated and fixed. After 800 c.c. of dextrose/saline, 8 mg. of Levophed and 2 ampoules of Isuprel were given. The patient blood pressure rose t 150/70 mm. Hg. The pulse was 130 and strong. The pupils ere no longer fixed ad dilated. The electrocardiogram (ECG) showed sinus tachycardia but as otherwise normal. The fundi showed no hemorrhages or exudate. The sclerae ere hite. The heart was enlarged nd short diastolic blow was heard ending ith S_3 along the left sternal border. The neck eins are distended. The liver was enlarged 4 finger-breadths below the costal margin. The abdomen as distended but paracentesis revealed no gross blood or fluid.

Laboratory examination revealed hematocrit 18 per cent (28 per cent the night before) hemoglobin 8.2 Gm. per 100 c.c. hite blood cell count 14 900 per cubic millimeter potassium 4.4 mEq. per liter sodium 145 mEq. per liter chloride 94 mEq. per liter pH 7.36, serum lactic dehydrogenase 6,050 units per milliliter (labile 84 per cent, stable 2 per cent) serum glutamic oxaloacetic transaminase 4,300 units per milliliter creatine phosphokinase 11 units per milliliter blood urea nitrogen 21 mg. per cent, creatinine 2.2 mg. per cent, and bilirubin, total 0.5 mg. per cent. A blood smear showed decreased platelets and some target cells. It as otherwise normal. Central enous pressure was 28 mm. Hg. Four blood samples were dra n. They were subsequently reported as showing no growth. At 2.00 p.m. 2 Gm. of Keflin, 0.8 mg. of Cedilanid and 2 units of packed red blood cells ere given. The patient continued to maintain her blood pressure and good urine output. On the same day Nov. 26, in the afternoon, cardiac catheterization as performed. The results are show in Table I. This as followed by cineangiogram. At 5.00 p.m. of the same day (Nov. 26) open cardiac surgery as performed. Three aortic cusps and 1.0 inch of ascending aorta ere excised. The aortic valv was replaced with Starr Ed ards prosthesis and the aorta with Teflon Ed ards graft. The heart was defibrillated but cardiac contractions were inadequate. The patient as pronounced dead in the operating room at 10.30 p.m.

Discussion

DR. GUNNAR One possibility I would like to el minate quickly is that the patient had some unrelated infectious process and cardiac arrest secondary to penicillin anaphylaxis. I would then have to explain the aortic insufficiency on the basis of a rupture of her aortic valve due to external massage. It usually takes an automobile accident or something of that nature to do this, and I suspect that is not what happened.

A second possibility that I must consider only to eliminate it is that the patient had a myocardiopathy and cardiac arrest secondary to the myocardial lesion. In a young woman who has had sudden cardiac arrest, myocardiopathy of some sort is a very likely possibility. In this patient I would consider two types of myocardiopathy. The first is associated with chronic use of some of the antidepressant agents, particularly phenothiazine derivatives. These agents can produce rather bizarre ECG changes and myocardial degeneration. The second type to be considered is nfectious. At the time of the year she was seen it could have been either a Coxsackie or influenzal infection with associated myocarditis.

A third possibil ty would be that she had been on birth control pills and in combination with prolonged hospitalization it was not pneumonia she had but the pain in her chest and the nfiltrate in her lung due to pulmonary embolism. The cardiac arrest would then be due to another episode of pulmonary embolism. We could account for the murmur on the basis of pulmonary valvular insufficiency. The murmur of insufficiency of the pulmonic valve tends to be along the left sternal border and frequently ends at the third sound. The murmur is shorter than the murmur of aortic insufficiency because the diastolic pressure in the pulmonary artery is closer to end diastolic pressure n the right ventricle than is aortic diastolic to the left ventricular end diastolic pressure. If pulmonic valvular insufficiency is very mild and/or pulmonary pressure is very high one can hear a long diastolic blowing murmur and this could fit with the murmur heard in this patient. The main difficulty with this diagnosis is that the patient did not have evidence

right ventricular strain She did not have the shift in axis on her ECG that one would expect with severe pulmonary embolism and pulmonic valvular insufficiency

A fourth possibility and the one the service I believe began to work with was that the patient had a pneumococcal pneumonia The bacteremia associated with the pneumonia had caused seeding of the aortic valve and she had developed an acute aortic insufficiency secondary to pneumococcal valvulitis. This complication of pneumococcal bacteremia is somewhat more frequent in upper lobe pneumonias but can be seen in any pneumococcal bacteremia. We have no evidence that she had pneumococcal bacteremia but I am not sure there were any blood cultures taken before she was treated with penicillin

If she had aortic insufficiency then it must have been severe. Mild aortic insufficiency causes a faint diastolic blow which is very slowly decrescent In other words it starts out high pitched and soft and the intensity of the murmur stays fairly constant throughout diastole until the first sound appears again and ends the murmur If one reports mild aortic insufficiency and a short blow I must assume that the murmur goes beyond the ability of the observer's ear to hear it because in mild aortic insufficiency the gradient between the aortic pressure and left ventricular pressure at beginning diastole and at the end of diastole has not changed markedly This small decrease in gradient should not cause a great loss in regurgitant flow It is possible to hear murmurs that start very faintly and then go beyond the ability to hear them otherwise a murmur of aortic insufficiency should not disappear in mid diastole unless the gradient also disappears. How does the gradient disappear? In severe aortic insufficiency the diastolic pressure in the aorta may fall off rapidly the diastolic pressure in the failing left ventricle builds up rapidly and in mid diastole there is equilibration of aortic pressure with the left ventricular pressure If you see a person with bacterial endocarditis who has a long diastolic blow that you think has recently appeared and you follow him during his course and that diastolic blow gets shorter and ends with a third sound he is not getting better he is getting worse. As a matter of fact it is at the end of the ability of the left ventricle to compensate.

The same holds for the pulse pressure. Part of the bounding pulse of aortic insufficiency is due to the peripheral vasodilatation but when the insufficiency gets severe and the heart is no longer able to have the rapid upstroke there is vasoconstriction and the pulse pressure becomes narrow again So as the aortic insufficiency gets worse the pulse pressure gets smaller and the murmur gets shorter The severity of the aortic insufficiency in this case was borne out by cardiac catheterization The aortic diastolic pressure was 39 mm. Hg and the left ventricular diastolic pressure was 35 mm Hg These pressures have essentially equilibrated in the middle of diastole. The only other laboratory examinations of interest were that the hemoglobin had decreased and for reasons that escape one It could have been hemolysis, but she was not jaundiced The white count was slightly elevated which would go along with any of the diagnoses we have talked about. The fact that she had an arrest and that she had external cardiac massage would account for enzyme changes and so all of these are essentially of little value at arriving at a diagnosis at this stage. Her central venous pressure was high which goes along with the fact that she was in cardiac failure The possibility remains, therefore that the patient developed acute aortic insufficiency secondary to pneumococcal valvulitis.

There is the history of chest pain but as described it was not particularly characteristic of dissection of the aorta although this is another possibility in a patient who develops acute aortic insufficiency The pain of aortic dissection may be diagnostic if it is acute and severe without increase in intensity Ordinarily it starts suddenly and then decreases. It tends to be sharp and lancinating and frequently travels up the neck vessels. This patient's pain may have been dulled by the fact that she had so much depressant medication It may be that the observer did not really try to get a history of whether the pain was of increasing or decreasing intensity We now need to see the angiograms.

DR. HARVEY O KAISER *Cineangiogram*— In tracing the contrast material with the catheter at the root of the ascending aorta, one can see that the left ventricle is filling completely There should not be any filling of the left ventricle when the aortic valves are competent. One can make out two main coronary arteries. The right appears to be patent. The left coronary artery is also visualized. There is contrast material entering the left atrium from the left ventricle, implying not only aortic insufficiency which is severe, but mitral insufficiency in addition probably from dilatation of the left ventricle. There is a peculiar area in the first portion of the ascending aorta where there seems to be a difference in density as the contrast material traverses it. Furthermore, it is associated with a rather jagged edge in place of the normally smooth flow of the material elsewhere in the ascending aorta. As for the aortic arch it seems ample possibly mildly dilated but not to the extent one sees in poststenotic dilatation.

DR. GUNNAR We now essentially have the diagnosis. That area of radiolucency in the cineangiogram is quite characteristic of a flap associated with the tear in a dissecting aneurysm and can account then for the aortic insufficiency The tear loosens up the aortic wall behind the attachment of the aortic valve and allows the cusp to fall in far enough so that quite marked aortic insufficiency develops. The apposition of the aortic valve is quite delicate and is really beautifully engineered. If however one valve loosens slightly it can invert and cause a good deal of aortic insufficiency We know the patient had marked aortic insufficiency not only from the pressures obtained by catheterization, but also from the angiogram. The insufficiency was so marked that it dilated the mitral ring and created mitral insufficiency I do not think we have to postulate that she had anything organically wrong with the mitral valve. If the dilatation of the ventricle proceeds far enough the papillary muscles are no longer able to permit the mitral valve to coapt properly I suspect I can account for her anemia, because there was probably a good deal of blood lost into the periaortic structures, or at least I am going to take that as my reason for the anemia. I have not really adequately explained why the fever and chills started so early It seems that that is out of proportion to what we found and that is still unexplained. I do not have a good reason to account for the tear in the aorta. It is possible that it could be traumatic. It is possible she could have medial necrosis, although there is no evidence that she had Marfan's syndrome. There is no other evidence to suggest that she had an arteritis which might account for her headaches (temporal arteritis) and then arteritis involving the aorta. She does not have a good history of hypertension. So we are really left with a group of patients who do have tears of the aortic root probably due to medial necrosis with no other manifestations of Marfan's syndrome.

STUDENT How then do you relate the injection of penicillin to the sudden cardiac arrest?

DR. GUNNAR I really cannot make the connection. It is unlikely even if the patient had cardiac arrest due to anaphylaxis that the aortic tear would be secondary to the trauma associated with resuscitation. It really takes a lot of trauma to do that. Even if at the time of injection there were no aortic insufficiency fright or the pain caused by the injection might have stimulated the sympathetic to produce a period of arrhythmia. If aortic insufficiency were present at that time, she would have been very prone to arrhythmias on the basis of a dilated ventricle.

DR. KARACHORLU At autopsy there were recent surgical incisions in the left inguinal right antecubital, and mid-chest regions due to recent cardiac surgery There was no peripheral edema. Each pleural cavity contained 500 c.c. of bloody fluid. There were no adhesions or inflammatory processes in the pleura or mediastinum. The peritoneal cavity contained 500 c.c. of clear fluid. The pericardium had been opened at the time of surgery There was hemorrhage into the parietal and visceral pericardia. The heart was markedly enlarged *in situ* It weighed 500 grams. The right atrium was normal including the endocardium, coronary sinus, fossa ovalis, and atrial appendage. The tricuspid valve measured

*Postdoctoral Trainee in Cardiology



Fig 1 View of the outflow tract of the left ventricle with prosthesis in place and with the Dacron graft replacing the first portion of the aorta Note the absence of endocardial fibrosis and pocketing and some dilatation of the left ventricle with myocardial hypertrophy

13 5 cm in circumference The leaflets of the tricuspid valve showed no pathologic change The chordae tendineae were thin and delicate The right ventricle was normal in size The thickness of its myocardium was 0 4 cm in the distal portion of the pulmonary outflow tract The pulmonic ring measured 7 cm in circumference The pulmonic cusps were normal The left atrium was not enlarged and its endocardium was not remarkable The mitral ring measured 12 cm in circumference The leaflets of the mitral valve showed some hemodynamic thickening The chordae tendineae were not remarkable The left ventricular cavity was moderately dilated Subendocardial hemorrhage was present throughout the entire endocardium However there was little endocardial fibrosis. There were no systolic or diastolic pockets. The left ventricular wall was thick measuring 1 5 cm near the base of the inflow tract The examination of the aortic ring showed the following findings The aortic cusps and first portion of the ascending aorta (2 5 cm in length) had been resected and a Starr Edwards valve was in place A Teflon graft occupied the resected portion of the aorta (Fig 1) The examination of the suture lines showed no evidence of leakage or thrombosis. The remaining portion of the aortic arch revealed no atherosclerosis dilatation ulceration thrombi fissures, or dissecting aneurysm The orifices of the coronary arteries were patent and arose normally The coronary arteries were not remarkable The histologic examination of the myocardium was not remarkable and that of the aorta immediately distal to the Teflon graft showed a normal intima media and adventitia However the resected aortic specimen showed the most important gross and histologic findings. It was submitted fixed in formalin and measured 2 5 cm in length and 6 4 cm in circumference (Fig 2) The wall of the aorta was very thick measuring 0 9 cm with seemingly marked fibrosis and some adventitial hemorrhage The intima presented multiple fissures extending into the media for a depth of 2 to 4 mm The base of the fissures was covered by whitish-gray fibrous-appearing tissue There were no vegetations but the intimal surface elsewhere had a dull and in places roughened appearance There was no true dissection and no real aneurysm Histologically the most striking findings were found in the media There were areas where the media was totally or partially necrotic either with little reactive inflammatory change or infiltrated by polymorphonuclear cells (Figs. 3 and 4) On the other hand there were necrotic areas of media with ingrowth of granulation tissue accompanied by acute and chronic inflammatory cells, including a rare multinucleated giant cell (Fig 5) Finally there were areas of media with considerable loss of elastic tissue and with extensive replacement by fibrous tissue (Fig 6) The intima over these affected areas was either relatively normal covered by some fibrin with or without polymorphonuclear cells, or slightly thickened by a highly cellular proliferate predominantly of fibroblasts. The adventitia by contrast was



Fig. 2 The resected sector of the aorta. Note the irregular deep fissures and the irregularity of the intimal surface.

markedly thickened by irregular often marked fibrosis, and by considerable interstitial edema. There was growth of granulation tissue through the adventitia and an accompanying infiltrate of lymphocytes, some plasma cells, and polymorphonuclears. The lymphocytes deep in the adventitia occasionally formed follicles with rarely secondary centers. The polymorphonuclears throughout the adventitia and necrotic media were of heterophile type with only a rare eosinophile. The vasa vasorum in instances were prominent with thick intimal coats containing longitudinally directed smooth muscle cells ("sperrarterien") and with narrow lumens. Neither they nor other small arteries of the adventitia showed evidence of recent or old inflammatory involvement. The base and lateral walls of the fissures were made up of granulation tissue with variable and at times more marked fibrosis (Fig 7) The base as a rule was within the adventitia.

The three aortic cusps seemed essentially normal grossly However microscopically there were subacute inflammatory changes in two of them in the area of attachment to the aorta. Stains for bacteria fungi spirochetes, and mycobacteria of the affected sector of the aorta and the valves failed to reveal the presence of any microorganisms.

The lungs were heavy The left lung weighed 500 grams and the right lung weighed 750 grams. The pleural surfaces were covered by thin fibrinous exudate. The pulmonary arteries were normal with no thromboemboli Grossly and histologically there was an acute bronchopneumonia with little evidence of chronic passive congestion. The liver weighed 1 750 grams. It showed the typical appearance of a nutmeg liver with histologically extensive very recent centrolobular necroses. The thoracic and abdominal aorta showed at best mild atherosclerotic changes both grossly and histologically The left kidney was normal and weighed 160 grams the right kidney weighed 130 grams and showed several scarred areas. These areas histologically were compatible with chronic pyelonephritis. Culture of heart's blood and lung at the time of autopsy grew *Aerobacter aerogenes* and *Pseudomonas aeruginosa* No pneumococci were recovered.

DR. KRAKOWER The lesion involving the short sector of the first portion of the aorta is a very unusual one The primary process appears to be one of necrosis of the media. This seemingly occurred in piecemeal fashion over a period of time, as evidenced by the range of reactive processes from recent necrosis with or without an acute inflammatory exudate to repair by granulation tissue and scarring The fissures, too are of longer standing They are unrelated to the resuscitative measures and probably occurred in an aorta rendered fragile by the intrinsic



Fig 3 Low power view of a section through the resected sector of the aorta The media is necrotic. Its elastic lamellae are clearly defined in its inner third The 2 heavy bands to the left represent necrotic media heavily infiltrated by polymorphonuclears. The remaining necrotic media shows little inflammatory cellular infiltration. The intima is somewhat thickened but infiltrated by polymorphonuclears. A strip of fibrin overlies it to the left. The adventitia is greatly thickened with granulation tissue coursing through it and with heavy infiltration by acute and chronic inflammatory cells. (Hematoxylin and eosin. × 200.)

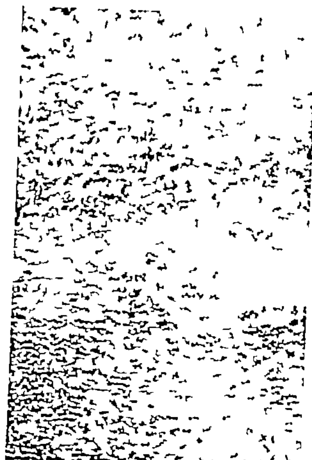


Fig 4 Enlargement of Figure 3 showing necrotic media infiltrated by polymorphonuclear cells. (Hematoxylin and eosin stain. × 500.)

necrotic and acute inflammatory processes. While there was some undermining of the fissures, there was no real dissection There was no intramural hemorrhage of consequence and no aneurysm There was a small amount of adventitial hemorrhage due to the operative procedures. In the absence of a clear history of hypertension the fact that the heart weighed 500 grams with a hypertrophic left ventricle would imply that there were abnormal hemodynamic changes prior to the onset of chest pain some 48 hours before death Certainly the inflammatory and reactive changes in the wall of the aorta and in the attached portions of the cusps of the aortic valve could have been responsible for a mild degree of aortic incompetence well before the short terminal event. The change from mild to severe aortic incompetence could have been occasioned by the respiratory and circulatory changes coincident with the development of acute bronchopneumonia and by the resuscitative measures. The absence of significant endocardial thickening and of a diastolic pocket in the outflow tract of the left ventricle need not militate against a milder degree of aortic insufficiency

The etiology and pathogenesis of this unusual aortic lesion are not clear It is not a bacterial or mycotic aortitis. Despite careful search no organisms were found It is not a syphilitic aortitis. The reactive changes are too acute in places. The vasa vasorum are free of endarteritic change The Venereal Disease Research Laboratory test was nonreactive It is not a localized form of polyarteritis nodosa hypersensitivity angitis or granulomatous angitis.



Fig. 5 An area of necrotic media partially acellular (top, right) and partially infiltrated by polymorphonuclears and mononuclears t the left ith ingrowth of granulation tissue from the adventitial side. (Hematoxylin and eosin. × 150.)

All these, aside from being multisystemic, tend to involve smaller vessels and are associated with fibrinoid necrosis of the vascular walls and often with appreciable eosinophilic infiltration. With hypersensitivity and granulomatous angiitis, particularly there is often an allergic history It is not a localized form of giant cell arteritis where the reactive processes are predominantly in the inner media and thrombosis is a common concomitant. Furthermore giant cell arteritis occurs in an older age group. It is not a localized angiitis related to systemic diseases such as lupus erythematosus, scleroderma, rheumatoid arthritis, or rheumatic fever There was no evidence for any of these diseases in the other tissues or organs. The medial necrosis and the inflammatory response to it, in the present case, have nothing in common with the mucoid degenerative changes of the media observed in medial necrosis of the Erdheim type or of Marfan's syndrome. It may be related to the 5 cases described by Mc Guire, Scott and Gall[1] the one case by Harvey Krakower and Roberg[2] the 6 cases by Isaacson and the 5 cases by Marquis and associates. All these are forms of chronic aortitis and arteritis. Except for one instance they are diffuse and nonsegmental They are of chronic proliferative character with little in the way of fresh necrosis of the media or acute inflammatory exudate. It may be mentioned in passing that in the case described by Harvey and his associates[2] there was clinically acceptable mild aortic regurgitation for a period close to 6 months and yet at the time of autopsy there were neither endocardial fibrosis nor diastolic pocketing of the outflow tract of the left ventricle. It may also be related to the chronic sclerosing aortitis of Takayasu's or pulseless disease. However the infarct-like medial necroses in the latter call forth a more granulomatous response rather than an acute or subacute inflammatory reaction Takayasu's disease affects predominantly young women heightening the resemblance to the present case. It clearly differs from



Fig 3 Low power view of a section through the resected sector of the aorta The media is necrotic. Its elastic lamellae are clearly defined in its inner third. The 2 heavy bands to the left represent necrotic media heavily infiltrated by polymorphonuclears. The remaining necrotic media shows little inflammatory cellular infiltration. The intima is somewhat thickened but infiltrated by polymorphonuclears. A strip of fibrin overlies it to the left. The adventitia is greatly thickened with granulation tissue coursing through it and with heavy infiltration by acute and chronic inflammatory cells. (Hematoxylin and eosin. × 200.)

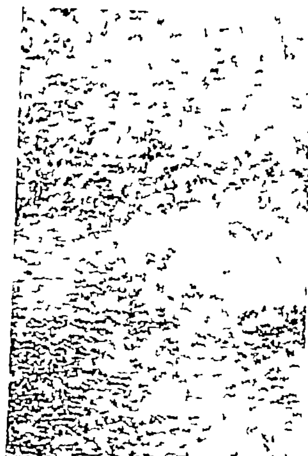


Fig 4 Enlargement of Figure 3 showing necrotic media infiltrated by polymorphonuclear cells. (Hematoxylin and eosin stain. × 500.)

necrotic and acute inflammatory processes. While there was some undermining of the fissures there was no real dissection There was no intramural hemorrhage of consequence and no aneurysm There was a small amount of adventitial hemorrhage due to the operative procedures. In the absence of a clear history of hypertension the fact that the heart weighed 500 grams with a hypertrophic left ventricle would imply that there were abnormal hemodynamic changes prior to the onset of chest pain some 48 hours before death Certainly the inflammatory and reactive changes in the wall of the aorta and in the attached portions of the cusps of the aortic valve could have been responsible for a mild degree of aortic incompetence well before the short terminal event. The change from mild to severe aortic incompetence could have been occasioned by the respiratory and circulatory changes coincident with the development of acute bronchopneumonia and by the resuscitative measures. The absence of significant endocardial thickening and of a diastolic pocket in the outflow tract of the left ventricle need not militate against a milder degree of aortic insufficiency

The etiology and pathogenesis of this unusual aortic lesion are not clear It is not a bacterial or mycotic aortitis. Despite careful search no organisms were found It is not a syphilitic aortitis. The reactive changes are too acute in places. The vasa vasorum are free of endarteritic change. The Venereal Disease Research Laboratory test was nonreactive It is not a localized form of polyarteritis nodosa hypersensitivity angitis or granulomatous angitis.

the present case, in that by definition, it involves the aortic arch and the ostial regions of the brachiocephalic arteries.

Accordingly the limited segmental nature and the subacute necrotizing character of the aortitis in the present case set it apart from all the other forms of aortitis that appear to have been described Even the case reported recently by Gloor[5] does not quite match the present one. The patient was a 21 year-old Caucasian man with pulmonary tuberculosis and diabetes who died of cerebral embolism and venous thrombosis 24 days after a right superior and middle lobectomy There was a lesion of the ascending aorta extending from the sinuses of Valsalva measuring 4.5 by 3.5 cm. There were areas of medial necrosis with no inflammatory infiltrate and areas of media which were being replaced piecemeal by granulation tissue with chronic inflammatory cells. The process could not be ascribed either to tuberculosis or to diabetes. Whether the present case represents a more acute inflammatory and segmental variant of the chronic aortitis described by McGuire and his associates or by Takayasu is clearly uncertain in the light of our ignorance with respect to the etiology and pathogenesis of these diseases.

STUDENT How would you explain the enlargement of the heart if the clinical data are accurate that aortic insufficiency first became apparent after the patient went into shock 12 hours before she died?

DR. GUNDKAR It is possible that the patient was hypertensive over a period of time but it remained undetected because she was so heavily sedated. It may be that the large heart could be accounted for on the basis of a hyperkinetic heart syndrome associated with schizophrenia. I am not sure that I would want to accept the cardiac enlargement on the basis of a mild aortic insufficiency existent over a longer period of time unless there were regurgitant pockets or a jet lesion of some type.

STUDENT In the absence of a true dissecting aneurysm how would you explain the anemia and the sharp drop in the hematocrit?

DR. GUNDKAR I have no way of explaining it. One would wonder whether with this type of lesion in the aorta there was sufficient turbulence of flow so that the red blood cells could have been injured However the description of the blood smear is not that of traumatized cells.

DIAGNOSIS *Subacute necrotizing segmental mesaortitis of undetermined etiology with terminal severe aortic insufficiency*

REFERENCES

1. McGuire, J Scott, R. C., and Gall, E. A.: Chronic aortitis of undetermined cause with severe and fatal aortic insufficiency Amer J Med. Sci. 226:394, 1955.
2. Harvey R. A., Krakower C. A., and Roberg N B. Clinical pathologic conference, Amer. Heart J 60:823 1960.
3. Isaacson, C.: An idiopathic aortitis in young Africans, J Path. Bact. 81:69 1961.
4. Marquis, Y Richardson, J B., Ritchie, A. C. and Wigle, E. D Idiopathic medial aortopathy and arteriopathy Amer J Med. 44:939 1968
5. Gloor E. Aortite idiopathique, Schweiz. Med Wschr 100 119 1970.



Fig 6 Collapsed and partially necrotic media is seen at the lower right with replacement of the media elsewhere by a fully developed collagenizing granulation tissue. (Hematoxylin and eosin × 250)



Fig 7 Section through a fissure with viable media (top left) and with collagenizing granulation tissue at the base of the fissure and its lateral wall to the right. (Hematoxylin and eosin. × 70)



Fig. 1. Intracardiac leads used for the study of intra-atrial, interatrial, atrioventricular and intraventricular activation.

great cardiac vein through the coronary sinus (BCSE) (Fig. 1) to record a local electrogram from the left atrium and the posterosuperior aspects of the left ventricle. The electrode leads were fed into a distribution switch box capable of obtaining any desired combination. The outputs of the distribution switch box were connected to the input of conventional electrocardiographic amplifiers and the signals filtered below 40 Hz. and above 500 Hz. A fourth bipolar catheter electrode with the same interelectrode distance was also introduced in the same fashion for intracardiac pacing. Recording of the three standard peripheral leads and a V precordial lead was carried out simultaneously with the intracavitary electrograms of the recording sites, using an oscillographic multichannel recorder* at a paper speed of 100 msec. The signals were simultaneously stored on a magnetic tape recorder for future playback.

The following intervals were measured (1) P R, as in conventional electrocardiography from the surface leads (2) A H from the onset of the atrial electrogram in the HBE leads to the His bundle deflection (3) H V from the His bundle deflection to the onset of ventricular depolarization, in which ever lead it occurred first (4) V A, from the beginning of the QRS complex (or the emission of the spike) to the atrial deflection in the HBE leads and (5) V LV and V RVT from the onset of the QRS complex (or the emission of the spike) to the local ventricular electrogram in the BCSE and HBE_{11} leads, respectively

The onset of the rapid deflections of the local electrogram was considered as the moment in which activation reached the fibers underlying the electrodes only in leads with interelectrode distance of 1 0 mm. With the methodology used there was a ±7 msec. interobserver variation in measurements.

*Electronics for Medicine Recorder DR-16, White Plains, N. Y.

Results

Atrial potential recorded by the BCSE. The use of BCSE for recording left atrial

Bipolar coronary sinus lead for left atrial and left ventricular recording

Agustin Castellanos, Jr., M.D.
Cesar A. Castillo, M.D.
Robert J. Myerburg, M.D.
Miami, Fla.

The use of transvenous pacing catheters is not without potential complications and problems. One of these, associated with a high incidence of failure to pace, is inadvertent passage of the catheter through the coronary sinus into a coronary vein.[1,2] The use of a routine posteroanterior chest x-ray film to diagnose this complication is often unreliable.[2] A superior location of the catheter tip between the left atrium and the posterobasal (or lateral) aspect of the left ventricle suggests passage into the great cardiac vein or beyond.[3] However, passage into the middle cardiac vein is more difficult to diagnose with a posteroanterior film, although a lateral view will demonstrate the posterior location of the tip.[3] Electrocardiographic diagnosis of malposition may be of some help. For instance, the mean QRS vector of paced ventricular beats when the catheter tip is in the great cardiac vein is inferiorly directed and associated with a right bundle branch block (RBBB) pattern due to delayed activation of the right ventricle,[4] while a middle cardiac vein location is indicated by left axis duration (due to inferior site of stimulation) and a RBBB pattern (due to the posterior location of the electrodes).[3]

Despite the fact that great cardiac vein catheterization is a troublesome complication for purposes of pacing, the intentional use of this technique for studies of human cardiac electrophysiology may prove to be quite useful. We are currently evaluating the use of coronary sinus and His bundle electrograms in analyzing the activation process of the human heart.

Methods

The technique of His bundle recordings used in our laboratory[5] is an extension of the one introduced by Scherlag and associates.[6] A tripolar catheter electrode* was introduced percutaneously through the femoral vein and positioned across the septal leaflet of the tricuspid valve under fluoroscopic control to obtain a His bundle electrogram (HBE) (Fig. 1). This electrode catheter had three poles—two separated by a 1.0 mm. distance (HBE_I) and the third pole 11 mm. from the first (HBE_{II}).* Two additional bipolar electrode catheters* with 1.0 mm. interelectrode distances[7] were introduced percutaneously through an antecubital vein. One of them was placed in the high right atrium (BAE) and the other one was introduced into the

From the Section of Cardiology, Department of Medicine, University of Miami School of Medicine and the Veterans Administration Hospital, Miami, Fla.
Reprint requests to: Dr. Agustin Castellanos, Jr., Section of Cardiology, Department of Medicine, University of Miami School of Medicine, P.O. Box 875, Biscayne Annex, Miami, Fla. 33152.
*Electrode Catheter Corporation, Rahway, N. J.

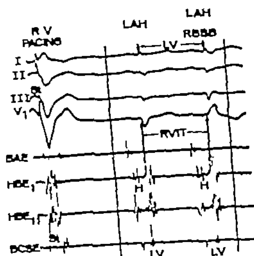


Fig. 3 Intraventricular activation during right ventricular apical pacing, pure LAH, and LAH with RBBB.

parently the slow waves seen in HBE and HBE which precede the sharp deflections indicating the onset of local activity were extrinsic in nature They could have been due to activation of the other sites distant from the recording electrode. This also occurred in HBE_1 indicating that it did not record exclusively local potentials. Hence the possibility that HBE leads can be influenced by mechanical events (movements of the tricuspid valves) cannot be excluded.

Discussion

The usefulness of the BCSE was established by observing that the local electrogram (representing activation of the posterosuperior region of the left ventricle) was activated early when an extrasystole was induced in this region and late when the ectopic beat originated in the right ventricular apex. On the other hand Fig 3 apparently indicated that during sinus rhythm the appearance of RBBB did not modify the moment in which the local electrogram was inscribed in the HBE lead The arrival of excitation did not appear to be delayed in the RVIT after the development of RBBB at least in patients with LAH The HBE leads cannot be used to determine the moment in which the RVIT is activated when there is considerable catheter movement produced by the motion of the tricuspid valve

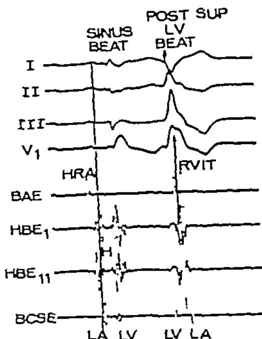


Fig. 4 Intraventricular activation pattern produced by an extrasystole originating in the posterosuperior region of the left ventricle.

leaflets. In these cases the corresponding bipolar lead will be distorted by mechanical artefacts (no matter how "close" the terminals are) Consequently a true "local" electrogram will not always be identified. Yet, Fig 4 shows that in some instances the HBE leads are valid for this purpose.

The term "RVIT" has been used in preference to the more elusive right ventricular base. Anatomists usually use the word base in reference to that part of the ventricles which is opposed to the apex and closest to the atria. In some descriptions of the general sequence of ventricular activation the right ventricular outflow tract has also been referred to as basal. Although the right ventricle has a triangular shape with the apex downward the other two angles which constitute the base are not at the same horizontal level The anteroposterior x-ray shows that the outflow tract is higher than the inflow tract. These three endocardial right ventricular regions have specific electrocardiographic patterns when paced. Pacing from the right ventricular apex produces a LBBB pattern with abnormal left axis deviation, with a vertical axis when the

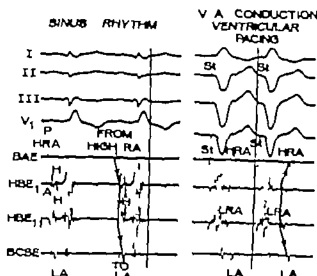


Fig 2 Intra-atrial and interatrial activation during sinus rhythm (left) and retrograde (V A) conduction (right)

activity and analyzing inter-auricular conduction is shown in Fig 2 The left panel is the control tracing from a patient with RBBB and left axis deviation due to left anterior hemiblock (LAH)[6] During sinus rhythm the high right atrium was activated before the low right atrium as shown by the onset of atrial activity in BAE before the beginning of atrial activity in HBE The atrial deflection in the BCSE lead appeared after the atrial deflections of both of the previous mentioned sites. Therefore the stimulus propagating from the sinus node reached the low right atrium before it reached that portion of the left atrium from which the BCSE was recorded

During retrograde (V A) conduction a different pattern of atrial depolarization occurred Atrial activity was initially recorded by the HBE lead (low right atrium) and later in the high right atrium and in the left atrium (BCSE lead) at more or less the same time. Thus a classical postulate of electrocardiography was supported i e the pathways that the impulse originating in the sinus node follows through the atria in its journey toward the A V node appears different from that used by a retrograde impulse. It should be re-emphasized that these results do not necessarily imply that the low right atrium is invariably activated before the left. The recordings only show that a region of the right atrium presumably close to the A V node was activated before the explored left atrial site.

Ventricular potentials recorded by the BCSE. The use of the BCSE for recording left ventricular activity and analyzing conduction patterns is shown in Figs. 3 and 4 The third (sinus) beat in Fig 3 shows complete right bundle branch block (CRBBB) and left anterior hemiblocks (LAH) The P R A H and H V intervals measured 140 45 and 40 msec. respectively The second beat, also of sinus origin shows LAH without RBBB The duration of the previously mentioned intervals did not change However QRS duration decreased from 150 to 90 msec. The first ventricular complex preceded by a stimulus artefact was obtained during right ventricular apical pacing It shows a left bundle branch block (LBBB) pattern with abnormal left axis deviation and a QRS duration of 155 msec. During pure LAH the local (left) ventricular electrogram occurred 45 msec after the onset of ventricular depolarization This corresponded to a point in the ascending portion of the R wave in Lead I (vertical arrows on top of the lead) Onset of electrical activity in this site was not delayed during RBBB However when the apex of the right ventricle was paced the local left ventricular electrogram was activated 120 msec after the emission of the spike This corresponded to a point on the terminal portions of the R wave in Lead I On the other hand ventricular activity in the HBE_1 which presumably recorded from the right ventricular inflow tract (RVIT) occurred 30 msec after the beginning of the QRS complex both during LAH and when LAH was associated with RBBB (vertical arrows below Lead V_1 Fig 4)

The second beat in Fig 4 is an extra systole induced by the catheter in the great cardiac vein It shows the characteristic pattern produced by stimulation of the posterobasal portion of the left ventricle[4] right axis deviation with a predominant positive deflection in V_1 QRS duration was 150 msec The local electrogram recorded by BCSE occurred at the onset of depolarization It should be noted that activation reached the inflow tract of the right ventricle 50 msec. later Ap-

Indications for temporary pacemaker insertion in acute myocardial infarction

Alfred J. Kaltman, M.D.
New York, N. Y.

During the past dozen years electrical pacing of the heart by means of a transvenously introduced endocardial electrode catheter has become an easily accomplished and widely employed procedure. The use of this technique as a temporary measure in the management of patients with acute myocardial infarction has received considerable attention. The opportunity for careful assessment of its value in the treatment of acute myocardial infarction has been furthered by experience gathered in monitoring data from various coronary care and cardiac monitoring facilities.

Early investigators were very aggressive in their approach. With time a more careful analysis of the natural course of myocardial infarction and the effects of pacemaker intervention has permitted a more selective attitude in the use of this modality. Accordingly it has assumed an important role in the management of various problems in the patient with acute coronary occlusion and myocardial infarction.

The major single indication for temporary transvenous cardiac pacing in myocardial infarction has been bradyarrhythmias with a deteriorating clinical state. Improvement of the patient with acceleration of the heart rate may be achieved by various drugs such as atropine or isoproterenol. Under some conditions these pharmacologic agents may be ineffective or contraindicated and artificial pacing may become a necessary factor in treatment.

Bradycardia may occur as a result of complete atrioventricular block, a slow sinus rhythm, or atrial fibrillation. Electrical pacing can be an appropriate method of controlling the ventricular rate in any of these instances.

Slow heart rates often are associated with ventricular irritability and ectopic rhythms. This is especially true during the early stages of acute myocardial infarction well-recognized for its electrical instability. Overdrive suppression of this ventricular irritability is possible by artificial cardiac pacing at a more rapid rate.

Repetitive atrial or ventricular tachycardias also have been suppressed by electrical pacing. This has been of particular value in acute myocardial infarction when rapid control is needed but repeated direct current electric shock conversions are undesirable. Artificial pacing may then permit the use of cardiac suppressive drugs or digitalis preparations in situations where the continued use of them might have been prejudicial. It may even be useful in ectopic rhythms associated with digitalis toxicity. Under these circumstances pacing may be

From the Department of Medicine, New York University Medical Center, New York, N. Y.

Received for publication Feb. 14, 1971.

base is paced and with a normal axis whenever the muscle of the RVIT is stimulated Moreover preliminary observations performed in our laboratory seem to indicate that recordings obtained from these sites yield patterns as specific as those described for stimulation

Although the explanation of the findings presented in this report requires further corroboration we believe that the technique should be evaluated further since it offers potential information regarding electrophysiological events occurring in the human heart Extrapolation from animal experiments important as it is requires caution as the historical events regarding the diagnosis of hemiblocks show [10]

REFERENCES

1. Castellanos, A. Jr and Lemberg, L. Electrophysiology of pacing and cardioversion New York, 1969 Appleton-Century Crofts, Inc. p. 12.
2. Meyer J A and Millar K. Malplacement of pacemaker catheters into the coronary sinus. Recognition and clinical significance, J Thorac Cardiovasc Surg 57:511 1969
3. Latour H. and Puech, P Electrocardiographie endocavitaire Paris, 1957 Masson & Cie, p. 17
4. Castellanos, A. Jr and Chapunoff E. The vectorcardiogram in left posterior hemiblock. Presented at the XI International Symposium on Vectorcardiography—Long Island Jewish Medical Center May 1970, New York, N Y
5. Castellanos, A. Jr Chapunoff E. Castillo, C et al.: His bundle electrograms in two cases of Wolff Parkinson-White (pre-excitation) syndrome, Circulation 41:399 1970.
6. Scherlag B J Lau S. H Helpant et al. Catheter technique for His bundle activity in man, Circulation 39:13 1969
7. Castillo, C. A. and Castellanos, A. Jr Retrograde activation of the His bundle during intermittent paired ventricular stimulation in the human heart Circulation. In press.
8. Rosenbaum M B Elizari M V and Lazzari, J V Los hemibloqueos pasdos, Buenos Aires, 1967 p. 206.
9. Sodi Pallares, D and Calder R. M New bases of electrocardiography St. Louis, 1956, The C. V Mosby Company p. 332.
10. Blocks in the left bundle branch—A law of science fulfilled, Letter to the editor Chest 57:198, 1970

at least transiently prevent cardiac arrest.

Because of the suddenness of onset of complete heart block and its serious prognostic implication in acute anterior wall myocardial infarction the use of an artificial pacemaker is justified at the earliest suggestion of the development of any atrioventricular or intraventricular conduction delay Limited success in survival with myocardial infarction is discouraging but it does offer some control in a desperate situation and should be considered an adjuvant to other medical and supportive measures. Under appropriate circumstances it may be used in conjunction with temporary heart bypass procedures or mechanical pump assistance.

Incomplete atrioventricular block

Some investigators advocated the early insertion of transvenous electrode catheters in all patients with first degree atrioventricular block. Congestive heart failure and the necessity for administration of digitalis or myocardial depressant drugs was considered a further indication On the other hand most patients with first degree heart block do not develop complete block. In those progressing to this stage especially with inferior wall myocardial infarction second degree atrioventricular block usually can be recorded as an intermediate stage and a decision for insertion of a pacemaker made at that time. Most observers, however would consider the prophylactic introduction of an electrode catheter with a standby demand pacemaker in patients with anterior wall myocardial infarction and the occurrence of even first degree atrioventricular block.

In general about a third of the patients with second degree atrioventricular block will progress to complete heart block. Atropine or isoproterenol may reverse this course and electrical pacing may not be necessary This is more likely in the Wenckebach or Mobitz Type 1 block usually associated with inferior wall myocardial infarction In anterior wall infarction there is a higher incidence of Mobitz Type 2 atrioventricular block and because of the more serious prognostic significance and resistance to drug therapy prompt prophylactic electrical pacemaker control is recommended

Overdrive suppression

The duration of the refractory period of the atria and ventricles is related directly to the cycle length With acceleration of the heart rate the refractory period is reduced the vulnerability threshold for development of ventricular fibrillation is raised, and ventricular ectopic beats become less frequent. Thus, by increasing heart rate with drugs or by electrical pacing one may inhibit ectopic rhythms.

Susceptibility to ectopic beats at slow heart rates occurs in sinus bradycardia and atrial fibrillation as well as in patients with complete heart block. The frequency of premature ventricular systoles early in the diastolic cycle even during repolarization suggests re-entrant excitation. Whether these ectopic beats are a result of re-entrant circuits or augmented Purkinje cell automaticity increasing the heart rate inhibits their initiation and propagation.

The electrical instability noted during the early stages of acute myocardial infarction with bradyarrhythmias and frequent ventricular premature systoles may be controlled by speeding up the heart rate with drugs such as atropine or isoproterenol If these are ineffective, atrial or ventricular electrical pacing may be useful This is especially of value in situations when there is a question of toxicity of digitalis or antiarrhythmic drugs, quinidine or procainamide

Overdrive suppression more recently has been employed to control recurrent rapid ventricular or atrial dysrhythmias in patients without complete heart block. Usually the rate of the overdriving pacemaker need not exceed that of the ectopic rhythm A rate slightly faster than the intrinsic sinus mechanism is sufficient. Rapid rates in excess of 100 beats per minute for long periods may complicate myocardial infarction with congestive heart failure. The concomitant use of myocardial depressants like procainamide or beta-adrenergic blocking agents may further reduce the necessary suppressive pacing rate. Electrical overdrive has become a useful mechanism for handling recurrent tachycardia refractory

used in conjunction with cardiac depressive agents.

Complete heart block

Between 6 and 8 per cent of patients admitted to coronary care units develop complete atrioventricular block. About 85 per cent of the heart blocks occur within the first 48 hours of observation usually they disappear within a week. Survival with persistent complete heart block requiring a permanent pacemaker is extremely rare. Differences in morbidity and mortality rates have been associated with the location of the infarct and the resultant varying mechanisms of development of the conduction disturbance.

Diaphragmatic or inferior wall myocardial infarction. In approximately 90 per cent of patients the artery to the atrioventricular node arises from a terminal branch of the right coronary artery. Proximal occlusion of this vessel usually causes ischemia and necrosis of contiguous myocardium rather than destruction of the conduction tissue itself. Infarction of the diaphragmatic region of the myocardium rarely extends far enough superiorly or anteriorly to involve the distal segments of the conduction system.

In more than 50 per cent of cases the sinus node artery also has its origin from the right coronary artery. This together with the fact that the inferior myocardial wall between the coronary sinus and the atrioventricular node is abundantly supplied with cholinergic tissue accounts for the high incidence of sinus bradycardia following acute occlusion of the right coronary artery.

Complete heart block rarely occurs abruptly during inferior wall myocardial infarction. It usually is ushered in by evolving first and second degree atrioventricular block often of the Wenckebach or Mobitz Type 1 pattern. The level of block within the junctional tissue is high usually above the His bundle resulting in a ventricular depolarization that is not usually prolonged and a heart rate between 50 and 60 beats per minute.

In the absence of complications such as shock syncope or congestive heart failure the survival rate of patients with inferior wall myocardial infarction and complete heart block is not significantly different from those without heart block. These complications impose a poor prognosis despite the intervention of electrical pacemakers. Artificial pacing is indicated if it can be demonstrated that acceleration of the heart rate per se is accompanied by an improvement in cardiac function. Objective measurements of cardiac output are helpful in this regard but usually we can be guided by clinical parameters such as regression of signs of shock or congestive failure and enhanced urine flow.

Anterior wall myocardial infarction. Complete heart block could be a result of prior or acute coexisting inferior wall myocardial infarction or disease of the conduction system of the heart. More commonly it is secondary to extensive necrosis of the interventricular septum due to occlusion of the anterior descending branch of the left coronary artery. There may be complete loss of the right bundle branch and partial destruction of the main or left bundle branch. The lower position of this necrosis usually below the bundle of His, causes a more prolonged and aberrant ventricular depolarization and slower idioventricular rate than that usually seen in diaphragmatic wall myocardial infarction.

The appearance of complete heart block may be sudden without the warning of first or second-degree incomplete block. Occasionally it may be preceded by a Mobitz Type 2 incomplete atrioventricular block or bilateral bundle branch block. Right bundle branch block is more common than left bundle branch conduction defects. Bilateral bundle branch block usually is manifested by early development of right bundle branch block and left anterior or posterior hemiblock.

Since the occurrence of complete heart block in anterior wall myocardial infarction is associated with extensive necrosis of tissue it often is complicated by shock and congestive heart failure. There is a high incidence of asystole with the acute development of right bundle branch or complete atrioventricular block. Prognosis for survival is poor even with pacing but electrical control of the heart rate may help maintain a falling cardiac output and

repeated electric shock conversion may be avoided in acute myocardial infarction.

Although the over-all effects of electrical pacing may not be as spectacular as originally speculated it has earned a definite but selective place in the management of patients with acute myocardial infarction.

REFERENCES

1. Stock, R. J and Macken, D L. Observations on heart block during continuous electrocardiographic monitoring in myocardial infarction, Circulation 38:993, 1968.
2. Norris, R. M: Heart block in posterior and anterior myocardial infarction, Brit. Heart J 31:352, 1969
3. Julian, D G., Lassers, B. W and Godman, M. J Pacing for heart block in acute myocardial infarction, Ann. N Y Acad. Sci. 167:911 1969
4. Lown, B and Kosowsky B D Artificial cardiac pacemakers, New Eng. J Med. 283:971 1970.
5. Lown, B., Klein, M D and Hershberg P L: Coronary and precoronary care, Amer J Med. 46 705 1969
6. Brown, R. W Hunt, D and Sloman, J G: The natural history of trioventricular conduction defects in acute myocardial infarction, Amer. Heart J 78:460 1969.

to pharmacologic intervention during the first few days following acute myocardial infarction

Technical considerations

When atrioventricular conduction is intact positioning of the electrode within the right atrium may be feasible Stimulation of ventricular dysrhythmias secondary to the mechanical placement of a catheter within the ventricle thus can be avoided Furthermore the hemodynamic benefits of sequential atrial and ventricular contraction can be maintained a decided advantage in the low cardiac output syndrome of acute myocardial infarction

Maintaining an atrial position of the catheter for long periods of time may be difficult. Special catheters have been used for atrial appendage wedging and other techniques have employed a coronary sinus location If this mode of pacing is unreliable ventricular placement of the catheter may become necessary

Electrical pacing can be instituted rapidly with introduction of a transvenous electrode by a percutaneous method This may be accomplished at the bedside without fluoroscopic control with the use of a flow-directed electrocardiogram monitored catheter via a subclavian or jugular route. A pre-existing central venous line may even accept a platinum wire that can be advanced into the heart. Percutaneous femoral or axillary routes or conventional cutdown antecubital approaches usually are more successful with fluoroscopic visualization This may be effected with a nearby or portable image intensifier Under other circumstances a patient may be transported to a cardiac catheterization laboratory but in acute myocardial infarctions bedside techniques are more desirable

The availability of the various methods of pacemaker insertion may play a part in the decision or timing for pacemaker use If image intensified fluoroscopy and trained personnel are at hand the introduction of a pacemaker electrode could be deferred until clear-cut indications are present However if only blind approaches with floating flow-directed catheters are available earlier use of these techniques may be permissible prophylactically because of the uncertainty inherent in these procedures and the necessity to avoid delay in urgent situations. With an electrode in place and a stand by pacemaker generator in a demand mode one is ready for emergency pacing

Conclusions

Although the effectiveness of emergency transvenous electrical pacing of the heart has been well established its impact on the prognosis of acute myocardial infarction is related to the location extent and complications of the underlying insult.

Inferior wall myocardial infarction with first or second degree atrioventricular block usually reverts to normal conduction spontaneously or with judicious drug therapy Even complete heart block may be transient and not require artificial pacing intervention If shock syncope or congestive heart failure complicate the picture a pacemaker may improve the clinical situation by accelerating the heart rate

The development of incomplete or complete heart block in anterior wall myocardial infarction usually is sudden and may be catastrophic. The prognosis is uniformly poor even with electrical pacing However a pacemaker may help control a deteriorating situation and should be used early in the course of acute anterior wall myocardial infarction as soon as any evidence of atrioventricular or intraventricular conduction delay is manifest.

The use of pacemakers in the electrically unstable early phase of acute myocardial infarction perhaps should receive more attention It may be helpful in the low output state by increasing systemic blood flow directly and by suppressing ectopic activity in bradyarrhythmias even in the absence of complete heart block Under these circumstances atrial pacing may be preferred

When pharmacologic intervention is unsuccessful or contraindicated overdrive suppression of atrial or ventricular tachycardias may be dramatic. Drugs that one might hesitate to pursue alone may be advanced more safely with the protective insurance of an indwelling artificial pacemaker The necessity for frequent or

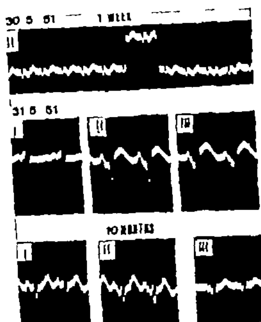


Fig. 2.

for periods of six and seven years, respectively. The presence of Wolff-Parkinson-White conduction after conversion of the tachycardias would seem to confirm the presence of an anomalous A-V bundle. All four cases agree with the observation of Nadas and co-workers[1] that the recurrence rate of tachycardias is low provided the first attack takes place before the fourth month of life.

If one accepts the existence of muscular A-V bundles as a normal stage in the development of the A-V ring, then it seems reasonable to suppose that at least some of the paroxysmal tachycardias in infants are directly related to the delayed development of the A-V ring during the first months of life. This type of arrhythmia then would have no significant chance of recurrence and would carry an excellent prognosis despite the initial severity of the syndrome.

Since direct proof of the above theory will be hard or impossible to obtain, further clinical evidence such as the exact documentation of the evolution of attacks of tachycardias in infants from other series will be required to test the validity of the hypothesis.

J. Roelandt, M.D.
Department of Cardiology
Medical Faculty Rotterdam
Rotterdam, The Netherlands
J. P. Roos, M.D.
Department of Cardiology
University Hospital
Leiden, The Netherlands

REFERENCES

1. Nadas, A. S., Daeschner, C. W., Roth, A., and Blumenthal, S. L.: Paroxysmal tachycardia in infants; study of 41 cases, Pediatrics 9:167, 1952.
2. Durrer, D., Schoo, L., Schuilenburg, R. M., and Wellens, H. J. J.: The role of premature beats in the initiation and the termination of supraventricular tachycardia in the Wolff-Parkinson-White syndrome, Circulation 36:644, 1967.
3. Cobb, F. R., Blumenschein, S. D., Sealy, W. C., Boineau, J. D., Wagner, G. S., and Wallace, A. G.: Successful surgical interruption of the bundle of Kent in a patient with Wolff-Parkinson-White syndrome, Circulation 38:1018, 1968.
4. Truex, R. C., Bishof, J. K., and Hoffman, E. L.: Accessory atrioventricular muscle bundles of the developing human heart, Anat. Rec. 131:45, 1958.

Serum uric acid, cholesterol, and cortisol intercorrelations in normoactive subjects*

In previous reports we presented a study of serum uric acid, cholesterol, and cortisol changes in Navy underwater demolition team (UDT) trainees during a 16 week training course.[1-3] There were significant shifts in the group means of all three serum measures, which correlated with periods of both psychological and physical stress. Although the subjects were a homogeneous group of healthy, young, adult men, and all were put through the same training stresses, the intercorrelations among uric acid, cholesterol and cortisol varied considerably from subject to subject. This finding was interpreted as indicative of a prominent "biochemical individuality" in these subjects' adaptation to the training program. In an attempt to elucidate the influence of the severe training situation on the intersubject variability of the inter-correlations among the three biochemical measures, we developed comparative data by performing inter-correlations on repeated serum uric acid, cholesterol, and cortisol measurements in normoactive, non-stressed, young adult men.

A number of clinical studies have indicated a relationship between increased levels of serum uric acid and serum lipids. The correlation between blood

*Report No. 69-38, supported by the Bureau of Medicine and Surgery, Department of the Navy, under Research Work Unit M4305.06-6001. Opinions expressed are those of the authors and are not to be construed as necessarily reflecting the official view or endorsement of the Department of the Navy.

Annotations

On the mechanism of paroxysmal tachycardias in neonates

Although paroxysmal supraventricular tachycardia is a relatively infrequent event in children, it has been noted that the syndrome is more likely to start before the fourth month of life than later It has also been noted that the younger the child the more likely that the arrhythmia has led to congestive heart failure and, therefore in infants, it is often an important problem. Furthermore, Nadas and co-workers in a series of 41 patients found a striking prognostic feature by noting that when the onset of the tachycardia took place during the first months of life the recurrence rate was 22 per cent, whereas when the attack occurred for the first time after the fourth month the recurrence rate rose to 83 per cent. While the etiology of these attacks is incompletely understood these observations do suggest that different mechanisms are at play

The coexistence of the Wolff Parkinson-White syndrome and paroxysmal supraventricular tachycardias is well known. The Wolff Parkinson-White syndrome has been demonstrated to coexist with an anomalous A V bundle and as a result, the supraventricular tachycardias are thought to be caused by "re-entry of impulses through this pathway This was clearly demonstrated by Durrer and associates[2] and further by Cobb and co-workers,[3] who proved that surgical division of the anomalous bundle reverted the ECG to normal while their patient was relieved of his tachycardia.

In this respect, it may also be relevant to quote the studies by Truex and associates[4] on the development of the A V ring. After the early embryonal stage, in which atria and ventricles still form one continuous muscle, fibrous tissue develops progressively between both structures. Just after birth, the annulus fibrosus was found to become fenestrated but, in their samples, complete separation of atria and ventricles did not take place until the sixth month of life. It, therefore, seems attractive to postulate that muscular A V connections of the type described by Truex may be the anatomical substrate for abnormal A V conduction, including the Wolff Parkinson-White syndrome and physiological tachycardias. The normal resolution of these anatomical pathways after the fourth month of life might explain the difference between the course of events in physiologic versus pathologic arrhythmia.

We recently observed an infant, one month old with a tachycardia of about 275 per minute (Fig. 1 upper strip) After triggered DC cardioversion, Wolff Parkinson-White conduction was present (middle strip) During hospitalization and under digoxin therapy the Wolff Parkinson White pattern remained unchanged.

Two months later normal sinus rhythm and normal A V conduction were present (lower strip) and have persisted until the present (age 17 months).

This observation led us to review our series of paroxysmal tachycardias in newborns. Three additional patients with the same clinical course were found. The first was observed in 1951 at the age of one week, with a tachycardia of 240 per minute (Fig 2, upper strip) After a trial with digoxin, sinus rhythm was restored but a Wolff Parkinson-White pattern was evident (middle strip) Ten months later normal sinus rhythm with a normal A V conduction could be demonstrated (lower strip) and was present for 19 years each time he was examined at the outpatient clinic.

The other patients were first examined at the age of five and seven weeks. In these the Wolff Parkinson-White conduction persisted until the sixth and eighth month respectively A V conduction became normal afterward and has remained so

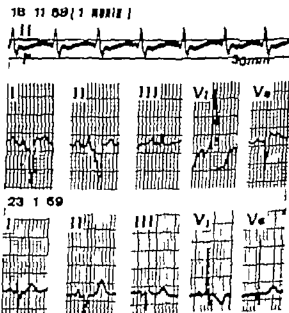


Fig. 1

correlations, and in the distribution patterns of these correlations (Fig. 1). All these data indicate that in future studies on the interaction of metabolic functions, consideration should be given to the use of longitudinal sampling and statistical design, and to the appropriate timing of sample collections.

Robert T. Rubin, M.D.
Brian R. Clark, A.B.
Russell E. Poland, A.B.
Ransom J. Arthur, Captain (MC) USN
Department of Psychiatry
U.C.L.A. School of Medicine
Los Angeles, Calif. 90024
Navy Medical Neuropsychiatric Research Unit
San Diego, Calif. 92152

REFERENCES

1. Rahe, R. H., Rubin, R. T., Arthur, R. J., and Clark, B. R.: Serum uric acid and cholesterol variability: A comprehensive view of underwater demolition team training, J.A.M.A. 206:2875, 1968.
2. Rubin, R. T., Rahe, R. H., Arthur, R. J., and Clark, B. R.: Adrenal cortical activity changes during underwater demolition team training, Psychosom. Med. 31:553, 1969.
3. Rubin, R. T., Rahe, R. H., Clark, B. R., and Arthur, R. J.: Serum uric acid, cholesterol, and cortisol levels: Interrelationships in normal men under stress, Arch. Intern. Med. 125:815, 1970.
4. Rubin, R. T., Rahe, R. H., Gunderson, E. K. E., and Clark, B. R.: Motivation and serum uric acid levels, Percept. Motor Skills 30:794, 1970.
5. Liddle, L., Seegmiller, J. E., and Laster, L.: The enzymatic spectrophotometric method for determination of uric acid, J. Lab. Clin. Med. 54:903, 1959.
6. Clark, B. R., Rubin, R. T., and Arthur, R. J.: A new micromethod for the determination of cholesterol in serum, Anal. Biochem. 24:27, 1968.
7. Clark, B. R., and Rubin, R. T.: New fluorometric method for the determination of cortisol in serum, Anal. Biochem. 29:31, 1969.
8. Florica, V., and Muehl, S.: Relationship between plasma levels of 17-hydroxycorticosteroids (17-OH-CS) and a psychological measure of manifest anxiety, Psychosom. Med. 24:596, 1962.
9. McNemar, Q.: Psychological statistics, ed. 4, New York, 1969, John Wiley & Sons, Inc., p. 158.
10. Rubin, R. T., Plag, J. A., Arthur, R. J., Clark, B. R., and Rahe, R. H.: Serum uric acid. Diurnal and hebdomadal variability in normoactive subjects, J.A.M.A. 208:1184, 1969.
11. Rubin, R. T., Plag, J. A., Clark, B. R., and Poland, R. E.: Diurnal and hebdomadal patterns of serum cholesterol in normoactive subjects. (Submitted for publication.)

Aortic declamping shock

Reconstructive measures on the abdominal aorta and iliac vessels, such as resection and replacement, bypass with graft, and thromboendarterectomy are frequent surgical procedures in most of the hospitals today. Temporary interruption of the aortic flow proximal to the level of reconstruction, usually below the level of the renal arteries, is prerequisite to such procedures. In majority of patients, this is accomplished without significant clinical manifestations of hemodynamic and metabolic changes. With improvements in anesthetic techniques and better understanding of the pathophysiology of declamping shock, fatal complications occur only rarely. However it should be recognized and emphasized as a serious threat in elderly and poor-risk patients subjected to major aortoiliac surgery.

Most of the patients undergoing aortoiliac vascular repair are in the sixth or seventh decade of life. Frequently such patients have associated cerebrovascular, coronary and myocardial, or renovascular disorders, although dormant. Therefore, precipitous fall in the systemic arterial pressure and impaired perfusion of vital organs, coupled with metabolic changes and anesthetic toxicity may lead to serious and sometimes fatal tragedies.[1-3] A large volume of blood is often sequestrated in the distal area with interrupted blood flow as a result of peripheral vascular dilatation.[1,4] Myocardial tissue with pre-existing damage or ischemic changes is particularly vulnerable to metabolic acidosis. Inadequate ventilation or impaired oxygen exchange may aggravate the situation. The successful management of the complications of aortic declamping is preferably by the cooperative efforts of the surgeon and anesthesiologist—preoperative evaluation and preparation as well as prophylactic measures rather than by the frantic attempts of the surgeon or the anesthesiologist alone, once the clinical manifestations have become obvious.

There is a diversity of opinion concerning the pathophysiology, frequency, prophylactic measures, and treatment of hypotension with aortic declamping. An abrupt release of the aortic clamp washes out a large hypoxic and acidotic distal vascular bed. Loss of volume into this crevice may be responsible for the sudden but temporary hypovolemia. The duration of occlusion, abruptness of declamping, sympathetic tone of the venous system, amount of collateral flow oxygenation, anesthetic agents, depth of anesthesia, presence of associated cardiorespiratory problems, and inadequate replacement of the

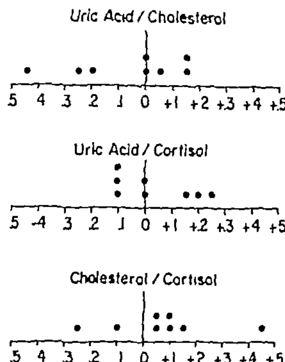


Fig 1 Patterns of distribution of intraindividual correlation coefficients among serum uric acid cholesterol, and cortisol for eight subjects.

levels of uric acid and cholesterol, however has been reported variously as positive, negative, or nonexistent.[3] Methodologic factors contributing to these disparate findings include the use of subjects of differing ages, sex, health status, and life situations, and the use of cross-sectional sampling designs. Only a few studies included two or more blood measurements on the same patients.

There appear to be no previous reports on the normal relationship between serum uric acid and cortisol. Three reports suggest a small positive correlation between serum cholesterol and cortisol, but again, these studies were done across subjects rather than intraindividually. Unlike the previous reports, our present study utilized a longitudinal sampling design.

Eight Navy corpsmen, ages 18 to 24 healthy and receiving no medications, served as subjects during their routine activities on an aircraft carrier. Diet was standard Navy fare. Blood was drawn for seven days at 0900 1500 and 2100 times were as widely spaced as possible without interfering with work-sleep cycles. The sera were immediately separated and stored at −20°C until analysis. Serum uric acid was determined by the method of Liddle, Seegmiller and Laster[4] serum cholesterol by the method of Clark, Rubin, and Arthur[5] and serum cortisol by the method of Clark and Rubin. The errors of measurement for these three methods, respectively were ±5 per cent, ±3 per cent, and ±2 per cent.

This sample population was homogeneous with respect to age sex, health status, and stability of life situation. The individual means of serum uric acid ranged between 5 10 and 7 98 mg per cent, and individual variabilities were 5 to 16 per cent of the individual means. Only one subject was statistically hyperuricemic (> 7 0 mg per cent) The individual means of serum cholesterol ranged between 155 and 254 mg. per cent and the individual variabilities were 6 to 12 per cent of the individual means. None of the subjects appeared to be consistently hypercholesterolemic. The individual means of serum cortisol ranged between 4 98 and 9.23 µg per cent, and individual variabilities were 42 to 61 per cent of the individual means. The range of cortisol means indicates that these men were experiencing little subjective psychological stress the mean values were comparable to the mid-afternoon plasma 17 hydroxycorticosteroid levels seen in low-anxious subjects.[8] The normal diurnal decrease of blood cortisol between 0900 and 2100 accounts for the large variabilities in this measure.

The intraindividual correlations among the three biochemical variables showed a fairly broad range of both positive and negative values. Individual correlations of uric acid with cholesterol ranged between +0 16 and −0.47 individual correlations of uric acid with cortisol ranged between +0.26 and −0.10 and individual correlations of cholesterol with cortisol ranged between +0.46 and −0.24 The average correlations,[9] on the other hand were all of low order and none was statistically significant. Fig 1 illustrates the distribution of each set of individual correlations. These data suggest that an across-subjects statistical analysis of intercorrelations among serum uric acid, cholesterol, and cortisol can mask the variation found in longitudinal, intraindividual correlations among these measures. This may help explain the conflicting results of the previous studies of serum uric acid–cholesterol relationships.[8]

The uric acid–cortisol and cholesterol–cortisol correlations appear to be the first such data presented on healthy nonstressed normoactive subjects. The correlations between uric acid and cortisol were generally of low order Cholesterol-cortisol correlations showed a somewhat greater range, with a preponderance of low positive values. This latter finding is consistent with the positive cholesterol cortisol relationships reported previously

Because the blood samples were drawn three times each day the uric acid and cholesterol values also were analyzed for possible diurnal variability.[10,11] Both uric acid and cholesterol showed statistically significant mean differences between subjects, but only uric acid showed a significant intraindividual diurnal variation. Phase differences in the diurnal patterns of uric acid, cholesterol, and cortisol from subject to subject may have contributed to the wide ranges of intercorrelations.

Our data suggest that even in a homogeneous group of healthy normoactive subjects under average work conditions there is an individuality in the intercorrelations of serum uric acid, cholesterol and cortisol. As mentioned we found similar differences in the individual patterns of these three measures in 20 UDT trainees under conditions of severe physical and psychological stress.[1] We had interpreted these findings as suggestive of a considerable individuality in the pattern of biochemical responsiveness and adaptation to stress. The results of the UDT study and the present one are consistent both in the ranges of positive and negative intraindividual

to aortic release, Surg Gynec. Obstet. 116:301 1963.

3. Montgomery H.: The circulation in the periphery in Green, H D., editor: Shock and circulatory homeostasis, New York, 1954, Josiah Macy Jr Foundation.
4. Stoner H. B., and Threlfall, C. J editors. Biochemical responses to injury Oxford, 1960, Blackwell Scientific Publications.
5. Strandness, D E., Parrish, D G., and Bell, J W.: Mechanism of declamping aortic shock in operations on the abdominal aorta, Surgery 50 488, 1961.
6. Thomas, T V Role of thromboendarterectomy and bypass graft in occlusive vascular disorders, Surgery 66:965, 1969
7. Vetto, R. M., and Brant, B.: Control of declamping shock, Amer J Surg. 116:273 1968.
8. Sweifach B. W Humoral vasoactive and other metabolic derangements in shock, *In* Green, H. D editor Shock and circulatory homeostasis, New York, 1951 Josiah Macy J., Foundation.

Regional viral service laboratories

The role of viral infections in cardiology is well known. The incidence of deaths from cardiovascular disease increases during the winter months. This is due in large part to infections, i.e., viral infections themselves, or viral infections primarily or secondarily associated with bacterial infections, or mixed viral and bacterial infections. In fact, the pathogenic relationship of bacterial and viral infections in man has yet to be determined in hospitals and clinics during illnesses. Viruses themselves infect the heart either alone or with bacteria as conditioning factors. However until facilities for routine virologic studies are made available, the many problems related to viral-induced diseases will remain unknown. Only bacteriology is available for diagnostic purposes in general hospitals. The importance and value of sufficient service in bacteriology is appreciated by all clinicians, and bacteriologic investigations in patients are used to advantage. The situation for virology however is quite different in the practice of medicine. Service in clinical virology is pathetically inadequate. In most instances the diagnosis of viral illness is made on a clinical basis. To meet the clinical needs there should be at least one *regional* service laboratory for every million people. Until such facilities are provided, the management of infections, especially virologic ones, will remain far from ideal. Patients will suffer physicians will be handicapped in their management of patients, and advancement in medical knowledge related to viral infections will be slow

At present, physicians frequently undertake bacteriologic studies in their patients. If a possible offending bacterium is found, further investigations cease. Infections with viruses could exist along with the bacteria and not be properly appreciated. One finds only what one searches. It is time that we search for viruses on as routine basis as we do for bacteria. What has been attributed to bacteria, the only organism investigated, may really depend on viruses to produce disease.

G E. Burch, M.D
Tulane University School of Medicine
New Orleans, La.

actual blood loss are some of the other factors that affect the frequency and severity.[4-7] Although any one of these factors may predispose to this catastrophe it is usually a combination of them that can be traced as the culprit.

Stoner and Threlfell[4] in their studies of tourniquet shock in rats, demonstrated marked biochemical responses to shock in the carbohydrate metabolism. There was an initial rise in blood sugar level and rapid fall in the late hemorrhagic shock resulting in circulatory failure, decreased oxygen consumption, and increased lactate-pyruvate ratios three to six hours after release of the tourniquet. In addition to the high levels of corticosteroids and high levels of hepatic glycogen, there was a significant role played by the release of epinephrine. Blood may become hypercoagulable and release small clots to block pulmonary and portal circulation. Autonomous or local and neurogenic buffer reflexes control the distensibility of the peripheral vascular bed particularly of the venous system in shock.[1] Part of the effective circulating blood volume is also lost into the skin, muscles, liver, or lung. During physiological conditions up to 40 per cent of the blood volume can be lost or gained in response to heat into the skin. Vasoconstriction, produced in shock ideally should have a favorable effect, but the clinical and experimental evidence suggests that the gain from the skin is lost into the regional muscles.[3] Careful investigation and study of the patients who undergo peripheral vascular procedures should provide more relevant conclusions in the future.

Proper selection of the operative procedure is of vital importance. The most expedient method with the least blood loss and tissue damage should be chosen, particularly for poor risk patients. The goal of excellent palliation can be achieved by a bypass graft as well as by a prolonged and meticulous endarterectomy. In the author's personal experience an abrupt release of the clamp, inadequate replacement of blood and fluid volume, uncorrected acidosis, and effects of anesthesia are the most important factors. Regional vasoconstrictors may be instilled into the distal vessels before the release of the clamp in order to decrease the vascular bed.

Adequate preoperative evaluation, preparation of cardiorespiratory systems, and correction of electrolyte and fluid imbalance are general principles applicable to all major surgical procedures. Monitoring of the electrocardiogram, arterial pressure, and central venous pressure are becoming increasingly popular among surgeons and anesthesiologists for patients undergoing major surgical procedures for cardiovascular disorders. A significant alteration of the central venous pressure from the baseline level for the particular patient is of immense value when rapid blood and fluid infusions are required. The relation of the P wave to the QRS complex, the changes in ST segment and T wave, and their correlation with changes in arterial pressure and venous pressure yield valuable information regarding the cardiac status. Patients who have been receiving prolonged digitalis and diuretic therapy may have an irritable myocardium from hypokalemia. Bradycardia is of the utmost seriousness even though it is frequently caused by increased vagal activity or the effects of anesthetic agents, such as succinylcholine and halothane, and can be controlled with small doses of atropine sulfate.

Sweifach[8] studied vascular changes during the compensatory stage in tourniquet shock in dogs and rats under pentobarbital anesthesia. In most instances anesthesia served as a predisposing factor which limited the compensatory response and hastened the onset of decompensatory reactions. Experiments with no systemic anesthesia demonstrated that the animals were resistant to decompensatory vascular activity. The initial compensatory effect of shock produced by such experiments is a reduction in blood volume, partly due to blood loss as well as sequestration of blood or plasma in different tissues. Once decompensation has occurred, further blood volume is trapped within the terminal vascular bed and venous channels. In their studies as little as 10 ml. of blood represented the difference between life and death in a dog weighing from 10 to 15 kilograms during the above phase.

Frequent communication with the anesthesiologist about the blood loss and clamping and declamping of the aorta is essential. After a prolonged occlusion an early warning should be given about the approximate time at which the surgeon is likely to release the clamp. The clamp should be gradually released and be prepared to be reapplied if the volume is inadequately replaced and buffering agents, such as sodium bicarbonate, have not been given. Mild alkalosis is better tolerated than acidosis, particularly by an irritable myocardium. Although measurement of blood pH, Po_2, and Pco_2 saturation are unnecessary in routine abdominal aortic surgery, they should be resorted to when considered helpful in the management.

Preclotting of the graft or the use of woven grafts will decrease significantly the blood loss from the interstices and may be critical in some patients, particularly those with religious objections to blood transfusions. Technical expediency could be achieved in patients with abdominal aneurysms and satisfactory femoral pulses by saving the aortic bifurcation and using a straight tube graft instead of a bifurcation graft. Peripheral vasoconstrictors should only be used cautiously because of adverse effects, even though they may temporarily provide a sense of security. In summary, a knowledge of the metabolic and hemodynamic changes of aortic declamping shock may be helpful in preventing an occasional disaster in aortoiliac surgery.

Thomas K. Thomas, M.D.
Assistant Professor
Departments of Surgery
Veterans Administration Hospital
Kansas City, Mo.
University of Kansas School of Medicine
Kansas City, Kan.

REFERENCES

1. Alexander, R. S.: Functional properties of blood vessels, *in* Green, H. D., editor: Shock and circulatory homeostasis, New York, 1953, Josiah Macy, Jr. Foundation.
2. Fry, W. G., Keltzer, W. F., Kraft, R. O., and DeWeese, M. S.: Prevention of hypotension due

to aortic release, Surg. Gynec. Obstet. 116:301 1963.

3. Montgomery H. The circulation in the periphery in Green, H. D. editor: Shock and circulatory homeostasis, New York, 1954 Josiah Macy J. Foundation.
4. Stoner H. B., and Threlfall, C. J. editors: Biochemical responses to injury Oxford 1960, Blackwell Scientific Publications.
5. Strandness, D. E., Parrish, D. G., and Bell J. W. Mechanism of declamping aortic shock in operations on the abdominal aorta, Surgery 50:488, 1961
6. Thomas, T. V., Role of thromboendarterectomy and bypass graft in occlusive vascular disorders, Surgery 66:965 1969
7. Vetto, R. M., and Brant, B.: Control of declamping shock, Amer J. Surg. 116:273 1968.
8. Sweifach, B. W., Humoral reactions and other metabolic derangements in shock, in Green, H. D. editor: Shock and circulatory homeostasis, New York, 1951 Josiah Macy J. Foundation.

Regional viral service laboratories

The role of viral infections in cardiology is well known. The incidence of deaths from cardiovascular disease increases during the winter months. This is due in large part to infections, i.e. viral infections themselves, or viral infections primarily or secondarily associated with bacterial infections, or mixed viral and bacterial infections. In fact, the pathogenic relationship of bacterial and viral infections in man has yet to be determined in hospitals and clinics during illnesses. Viruses themselves infect the heart either alone or with bacteria as conditioning factors. However until facilities for routine virologic studies are made available, the many problems related to viral-induced diseases will remain unknown. Only bacteriology is available for diagnostic purposes in general hospitals. The importance and value of sufficient services in bacteriology is appreciated by all clinicians, and bacteriologic investigations in patients are used to advantage. The situation for virology however is quite different in the practice of medicine. Service in clinical virology is pathetically inadequate. In most instances the diagnosis of viral illness is made on clinical basis. To meet the clinical needs there should be at least one regional service laboratory for every million people. Until such facilities are provided, the management of infections, especially virologic ones, will remain far from ideal. Patients will suffer physicians will be handicapped in their management of patients, and advancement in medical knowledge related to viral infections will be slow

At present, physicians frequently undertake bacteriologic studies in their patients. If a possible offending bacterium is found, further investigations cease. Infections with viruses could exist along with the bacteria and not be properly appreciated. One finds only what one searches. It is time that we search for viruses on as routine a basis as we do for bacteria. What has been attributed to bacteria, the only organism investigated, may really depend on viruses to produce disease.

G. E. Burch, M.D
Tulane University School of Medicine
New Orleans, La.

Announcements

THE FIFTH ANNUAL WORKSHOP IN ELECTROCARDIOGRAPHY sponsored by the Rogers Heart Foundation, will be held at the Tides Hotel and Bath Club St. Petersburg Fla. June 14 through 18 1971 The director is Henry J L. Marriott, M D

For further details write the Rogers Heart Foundation, St. Anthony's Hospital St. Petersburg, Fla. 33705

THE TWENTY SEVENTH BRAZILIAN CONGRESS OF CARDIOLOGY will be held in Brasília, Brazil, from July 11 to 17 1971 The Executive Committee of the Congress is as follows President, Dr Luciano Vieira Secretary Dr Fran Teixeira Gonzaga Lima; Treasurer Dr Luís Vieira de Carvalho.

Author index*

January, pp. 1-148; February, pp. 149-298; March, pp. 299-446; April, pp. 447-582; May, pp. 583-734; June, pp. 735-864.

Announcements

THE FIFTH ANNUAL WORKSHOP IN ELECTROCARDIOGRAPHY sponsored by the Rogers Heart Foundation will be held at the Tides Hotel and Bath Club St. Petersburg Fla. June 14 through 18, 1971 The director is Henry J L. Marriott, M D

For further details write the Rogers Heart Foundation, St. Anthony's Hospital St. Petersburg, Fla. 33705

THE TWENTY SEVENTH BRAZILIAN CONGRESS OF CARDIOLOGY will be held in Brasília, Brazil, from July 11 to 17 1971 The Executive Committee of the Congress is as follows President, Dr Luciano Vieira Secretary Dr Fran Teixeira Gonzaga Lima Treasurer Dr Luís Vieira de Carvalho.

S

S

Subject index*

*January, pp. 1-148; February, pp. 149-298; March, pp. 299-446; April, pp. 447-582; May, pp. 583-734; June, pp. 735-844.

J

L

M

N

O

P

Q

R

S